

PATHOLOGY OF TUMOURS

<i>AFRICA</i>	BUTTERWORTH & CO (AFRICA) LTD DURBAN 1 LINCOLN S COURT MASONIC GROVE
<i>AUSTRALIA</i>	BUTTERWORTH & CO (AUSTRALIA) LTD SYDNEY 80 CONNELL STREET MELBOURNE 430 BOURKE STREET BRISBANE 240 QUEEN STREET
<i>CANADA</i>	BUTTERWORTH & CO (CANADA) LTD TORONTO 1367 DANFORTH AVENUE
<i>INDIA</i>	BUTTERWORTH & CO (INDIA) LTD BOMBAY BANK OF BARODA BUILDING APOLLO STREET FORT
<i>NEW ZEALAND</i>	BUTTERWORTH & CO (AUSTRALIA) LTD WELLINGTON 49/51 BALLANCE STREET AUCKLAND 35 HIGH STREET

PATHOLOGY OF TUMOURS

[R. A. WILLIS]

DSc MD FRCP

*SIR WILLIAM H. COLLINS PROFESSOR OF HUMAN AND COMPARATIVE PATHOLOGY
ROYAL COLLEGE OF SURGEONS LONDON*

*FORMERLY PATHOLOGIST TO THE ALFRED HOSPITAL CONSULTANT PATHOLOGIST TO THE AUSTIN
HOSPITAL FOR CHRONIC DISEASES AND LECTURER ON THE PATHOLOGY OF TUMOURS IN THE
UNIVERSITY OF MELBOURNE AUSTRALIA*

LONDON

BUTTERWORTH & CO (PUBLISHERS) LTD

BELL YARD, TEMPLE BAR

1948

To my wife Margaret

PREFACE

THIS BOOK is the outcome of my special interest in tumours during 20 years as a hospital pathologist. Most of the material on which it is based was studied in the pathology laboratories of the Alfred Hospital Melbourne between the years 1930 and 1945 and some of the work was written in this period during part of which I held also a research appointment in the Pathology Department of the University of Melbourne. In a great measure, then the book is a Melbourne product. Yet I am fortunate in my present post at the Royal College of Surgeons in that this is in part a research appointment so that during the past two years in addition to carrying out routine duties in the restoration of the museum and in teaching I have also been able to complete the present work. A few comments regarding the contents are necessary.

General scope of the work—While aiming to give a useful general outline of each topic I also wished the book to be a personal record of my own observations and conclusions. Throughout therefore I have used my own material as fully as possible and have introduced many brief reports of personally studied cases illustrative of the subjects under discussion. For the same reason I have made frequent reference to my own published papers and to my earlier book, 'The Spread of Tumours in the Human Body' the contents of which in many ways supplements that of the present larger work. On controversial matters too while indicating that they are controversial, I have preferred to avoid non committal vagueness and to state plainly my own present opinions even though these may have to be modified in the light of future experience.

The book is addressed primarily to pathologists, research workers and senior students but I am not without hope that clinicians also may find it useful and that even elementary students may find it intelligible. My conviction that much has yet to be learnt from the comparative pathology of tumours is shown by a chapter on this subject in Part I and by sections devoted to it in the chapters of Part II.

Illustrations—The figures are all from personally studied material and most of them have not previously been published. With few exceptions they are microphotographs. Illustrations of gross type specimens are unnecessary for those to whom the book is addressed and indeed are often not very instructive even for elementary students who will learn much more from actual specimens at operations and necropsies and in the museum. In selecting the figures I have often omitted those illustrating the well known appearances of common tumours such as are to be found in nearly every text book. I have preferred rather to show less familiar and special features and particularly the range of structural possibilities in tumours of the less common kinds. I have tried also to avoid needless reduplication of figures showing similar structural types of growth e.g. since the range of structure of squamous cell carcinoma is adequately illustrated for tumours of the skin and oral cavity I have given few or no illustrations of this type of growth in the oesophagus, uterus, vulva and penis. Most of the figures

are from cases reported in the text, and the legends often supplement the text descriptions. Except where the legends state that special stains were used the figures were prepared from paraffin sections stained by one or another of the ordinary haematoxylin methods. The magnification of all figures is given.

References—The reference lists given at the ends of the chapters are far from complete, I know that I have omitted many important references which might have been preferable to some of those included. To the writers of important papers which are omitted, I tender my apologies. My excuse is that no man can possibly read more than a small fraction of the literature on even a small section of the subject, and I have preferred to base my discussion on what I have read or at least consulted. For a writer to give long lists of references to papers he has not seen is always futile and often dishonest. On controversial matters I have tried to select my reading impartially, but I am well aware that I may not always have succeeded in this. Whatever omissions I may be guilty of in my reference lists I can at least claim that they comprise works which, with very few exceptions, I have personally consulted in the original. Works listed in bold type are those which I have found particularly useful as marking important discoveries or as good reviews with useful lists of further references, or for other reasons which I have in many instances stated in parentheses.

Acknowledgments—My happy association during 15 years with the members of the medical and surgical staff of the Alfred Hospital—too many to mention all by name—placed me deeply in their debt for stimulating discussions in ward and laboratory and for free access to the records of their cases. Individual acknowledgment is made in the text to those who have permitted me to record the histories of privately treated patients. With pleasure I express also my indebtedness to Professor P. MacCallum, of the University of Melbourne, with whose Department I was happily associated as a research worker for nearly 18 years.

Many others of my fellow pathologists, both in Australia and Great Britain, have helped me by the exchange of specimens and ideas, I can thank them only collectively for they are too numerous to name. But I must record my special indebtedness to two of them. Most of my manuscript was read by Professor G. W. Nicholson, formerly of Guy's Hospital, who made many valuable suggestions and criticisms. Those who value his writings as highly as I do will understand how privileged I feel to have had such a mentor. My second special debt is to Dr. Leila M. Hawksley, formerly pathologist to the Cancer Hospital, London, who has given me many valuable specimens of unusual tumours, especially of the gonads, bones and muscles, and who has helped me to clarify my ideas on many debatable points.

The dedication of this book to my wife, Margaret Willis, is more than usually appropriate, for not only has she given unstinted wifely encouragement to studies which meant surrender of many of our accustomed pleasures, but she also made many of the microscopical preparations, aided in many dissections and took some of the photographs. I record with pleasure my special thanks to Mr. Reg Prosser, of the Alfred Hospital Pathology Department, for his expert preparation of many thousands of microscopical sections, to Mr. Frank Watson of the Buckston Browne Research Farm, for his preparation of the majority of the microphotographs, to my secretary, Miss Patricia Leicester, whose efficiency and enthusias

CHAPTER I

DEFINITION OF TUMOUR

DEFINITION

It is ~~very~~ necessary to state that in this work the word *tumour* is used in the permitted or specific sense of a true neoplasm and not in its ancient and general sense of any localized swelling which included also inflammatory and reparative processes, hyperplasias, simple cystic swellings and malformations. Indeed, the task of this chapter will be to determine in what ways true tumours or neoplasms differ from all of these.

In his admirable Erasmus Wilson Lectures in 1925, Nicholson maintained that it is impossible to define a tumour. Wherever we look we see that tumours exhibit no differences in kind but only differences in degree—and these often the slightest—from the other tissues of the body. I have tried for years to formulate a definition but have failed. Others have been bolder. I will not weary you with their definitions, every one of which breaks down at one or more points. In spite of this deterring statement by one whose knowledge and judgement demand the greatest respect I nevertheless shall essay a definition. I believe that it is possible to frame a satisfactory definition avoiding the grosser defects of some previous attempts and clarifying by explanatory notes those obscurities which the very brevity of defining creates.

A tumour is an abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change.

ANALYSIS OF THE DEFINITION

(1) "An abnormal mass of tissue"

The essential tissue of a tumour is the actively growing cells of a specific kind or kinds which comprise the tumour proper, as distinct from incidental cells of other kinds which form the stroma of the growth or which are due to secondary inflammatory or phagocytic reactions. Thus the essential tissue of a myoma is its muscle fibres; its connective tissue strands and blood vessels are merely the supporting and vascular framework of the tumour tissue proper. So also in a malignant tumour, for example a scirrhus carcinoma of the breast although wide areas of the growth may consist of much dense fibrous tissue with only scattered groups of epithelial cells, there is no doubt that these cells only have suffered neoplastic change, and that the excessive fibrous tissue results from the tumour tissue of the uterus is in the stroma. In tumours, then, as in normal tissues, the parenchyma or tumour tissue proper is distinct from stroma, connective and related tumour and vascular tissues. In a carcinoma of the prostate the neoplastic tissue consists of cells of a single kind derived from the epithelium of the gland. Tumour classification and nomenclature are largely based on this fact. Thus a myoma is a tumour whose parenchyma consists of muscle fibres only; a chondroma is composed solely of cartilaginous tissue.

TABLE OF CONTENTS

Chapter

- 39 Tumours of the adrenal cortex
- 40 Tumours of the parathyroid glands
- 41 Introduction to mesenchymal tumours, fibroblastic tumours and myxomas
- 42 Tumours of adipose tissue
- 43 Tumours of cartilage and bone
- 44 Tumours of synovial tissues
- 45 Angiomas tumours and tumour like overgrowths of vascular tissue
- 46 Meningioma or arachnoid fibroblastoma
- 47 Leiomyoma and leiomyosarcoma
- 48 Rhabdomyoma rhabdomyosarcoma, and rhabdomyoblastic mixed tumours
- 49 Tumours of lymphoid tissue
- 50 Plasmacytomas and myelomatosis
- 51 Other neoplasms of haemopoietic tissues
- 52 The gliomata
- 53 Papillary tumours of the choroid plexus
- 54 Neurilemmoma and other tumours of nerve sheaths
- 55 Neuroblastoma and ganglioneuroma
- 56 Tumours of chromaffin tissues and of the carotid and aortic bodies
- 57 Neuro ectodermal tumours of the retina and ciliary body
- 58 The melanomata
- 59 Chordoma
- 60 Embryonic tumours of kidney and liver and general comments on embryonic tumours
- 61 The teratomata
- 62 Chorion epithelioma

Margaret Willis 1955
privately engraved

June 1955
Ep. ally
33 33

PREFACE

vii

greatly lightened the task of preparing the manuscript, and to Mr W R Le Fanu, Librarian to the College, and his staff for much bibliographic help under difficult conditions

For permission to reproduce from my published papers Figs 2-7, 12 13 286, 301 and 302, I am indebted to the Editor of the *American Journal of Cancer* and of *Cancer Research*. The Editor of the *Journal of Pathology and Bacteriology* kindly permitted me to reproduce Figs 39-41 167, 189 382 454 464-468 470 171, 473 475 477-490, 492 and 493. Figures 185-188 309 312 and 386 are reproduced by permission of the Editor of the *Medical Journal of Australia*. An author could not wish for greater consideration and courtesy than my Publishers have given me

LONDON May 1947

RUPERT A WILLIS



LIST OF ILLUSTRATIONS

FIG		PAGE
1	Age distribution of carcinoma necropsies ~ ~ ~ ~ ~	79
2	Vertical section of squamous cell carcinoma of dorsum of hand of a tar worker ~ ~ ~ ~ ~	107
3	Vertical section of squamous cell carcinoma of dorsum of wrist ~	108
4	Vertical section of squamous cell carcinoma of neck ~ ~	108
5	Vertical section of one half of squamous cell carcinoma of pinna ~	109
6, 7	Cancerous varicose ulcer ~ ~ ~ ~ ~	111
8	Superficial epidermoid carcinoma of a sinus of the buttock ~ ~	112
9	Small basal cell carcinoma of the cubital fossa ~ ~ ~	112
10	Sub epidermal basal cell carcinoma of the leg ~ ~ ~	113
11	Multiple superficial basal cell carcinomas of the skin ~ ~ ~	113
12	Sagittal section of carcinoma of lip ~ ~ ~ ~ ~	114
13	Vertical section of early carcinoma of tongue ~ ~ ~	115
14	Early recurrent carcinoma of tongue following radium treatment ~	116
15	The shape of a tumour as determined by its mode of origin ~ ~	122
16	Squamous metaplasia in endometrial adenocarcinoma ~ ~ ~	127
17	The range of structure in a carcinoma of the breast ~ ~ ~	128
18	Spindle-celled carcinoma of tongue ~ ~ ~ ~ ~	130
19	Pseudo glandular appearances in squamous cell carcinoma ~ ~	130
20	Clear celled pseudo glandular cystic structure in a glycogen rich epidermoid carcinoma of the skin ~ ~ ~ ~ ~	131
21	From an hepatic metastasis of a carcinoma of the tonsil showing numerous mitoses ~ ~ ~ ~ ~	133
22	High power views of mitoses ~ ~ ~ ~ ~	134
23	Mitoses in tumour cells from a rapidly growing tumour of soft tissues of thigh ~ ~ ~ ~ ~	135
24	Cellular pleomorphism and mitosis in an anaplastic tumour of the lung probably a fibrosarcoma ~ ~ ~ ~ ~	135
25	Skiagrams of bones containing metastases of carcinoma of the bladder ~	137
26	Astrocytosis at the margin of a metastasis of mammary carcinoma in the brain ~ ~ ~ ~ ~	138
27	A metastasis of anaplastic carcinoma of parotid gland in lung ~ ~	148
28	Interstitial infiltration of muscular coat of small intestine by argentaftin carcinoma ~ ~ ~ ~ ~	151
29	Interstitial infiltration of wall of a vein by spheroidal-cell carcinoma of breast ~ ~ ~ ~ ~	152
30	Invasion of skeletal muscle fibres by carcinoma of lung ~ ~ ~	153
31	Permeation of perineural lymphatics by spheroidal-cell carcinoma of breast ~ ~ ~ ~ ~	154

FIG		PAGE
32	Permeation of perineural lymphatics by adenocarcinoma of stomach -	155
33	Permeation of perineural lymphatics by adenocarcinoma of gall-bladder - - - - -	156
34	Permeation of large lymphatics in wall of duodenum by adenocarcinoma of stomach - - - - -	157
35	Thrombus formed over area of invasion of lumen of a main hepatic vein by a metastasis of carcinoma of lung - - - - -	158
36	Section of a large thyroid vein invaded by a metastasis of renal carcinoma in the thyroid - - - - -	159
37	Permeation of small veins in the myometrium by spindle celled epidermoid carcinoma of cervix - - - - -	160
38	Lumen of a main pulmonary artery invaded by carcinoma of the lung -	161
39, 40	Invasion of the perivascular spaces of the brain by a diffuse tumour of the lepto meninges - - - - -	162
41	Invasion of the perivascular spaces of the brain by a diffuse tumour of the leptomeninges - - - - -	163
42	Intra alveolar spread of a metastasis of carcinoma of bladder in lung -	163
43	Metastasis of papillary carcinoma of ovary in a lymph gland - -	166
44	Metastatic signet ring cell carcinoma of stomach in peripheral sinus of a lymph gland - - - - -	167
45	Free tumour embolus from carcinoma of liver in a pulmonary artery	173
46	Tumour emboli from carcinoma of bladder arrested in pulmonary arterioles - - - - -	174
47	Tumour embolus from carcinoma of duodenum arrested in a pulmonary arteriole - - - - -	175
48	Clumps of signet ring tumour cells in pleural fluid, from carcinoma of lung - - - - -	180
49	Clumps of tumour cells in pleural fluid - - - - -	181
50	A heavy deposit of signet ring carcinoma cells in ascitic fluid - -	182
51	Fibro adenoma of dog's breast showing intra canalicular structure -	211
52	Fibro adenoma of dog's breast showing glandular tissue and cartilage in close juxtaposition - - - - -	211
53	Fibro adenoma of dog's breast containing cartilage and bone - - -	212
54	Fibro adenoma of rat's breast - - - - -	213
55	Intra canalicular fibro adenoma of breast - - - - -	214
56	Intra canalicular fibro adenoma of breast - - - - -	215
57	Intra canalicular fibro adenoma of breast with hyalinization of connective tissue - - - - -	216
58	Fibro adenoma of breast showing hyalinization of connective tissue and atrophy of epithelium - - - - -	217
59	Giant fibro adenoma of breast - - - - -	218
60, 61	Giant fibro adenoma of breast - - - - -	219
62	Giant fibro adenoma of breast - - - - -	220
63 64	Giant fibro adenoma of breast - - - - -	221
65	Multi radicular papillary growth in a cystic mammary duct - - -	222
66	Multifocal carcinoma in widely separate parts of the breast - -	231
67	Early intra ductal mammary carcinoma - - - - -	234

FIG		PAGE
68	Intra ductal mammary carcinoma of cribriform type - - -	235
69, 70	<i>Detail of Fig. 68</i> - - - - -	236
71	Intra ductal mammary carcinoma in an area of cystic hyperplasia -	237
72, 73	Breast ductules distended by carcinoma - - - -	238
74	Scirrhus spheroidal celled <i>carcinoma simplex</i> of the breast -	239
75	Cellular spheroidal-celled <i>carcinoma simplex</i> of the breast -	239
76	A lymph nodal metastasis of signet ring-cell carcinoma of breast -	240
77, 78	Cornifying squamous-cell carcinoma of breast - - -	241
79, 80	Intra ductal carcinoma of male breast - - - -	247
81	Intra ductal carcinoma of male breast - - - -	248
82	Paget's disease of nipple - - - - -	249
83, 84	Paget's disease of nipple - - - - -	250
85, 86	Paget's disease of nipple - - - - -	251
87, 88	Paget's disease of nipple - - - - -	252
89, 90	Paget's disease of nipple - - - - -	253
91, 92	Intra ductal carcinoma accompanying Paget's disease of nipple -	254
93	Adamantinoma-like structure in carcinoma of sebaceous cyst -	262
94	Cystic adenoma of sweat glands of dog - - - -	263
95	Para-anal tumour of dog - - - - -	264
96	Glandular tumour from skin of chest of dog - - -	264
97	Sub-epidermal basal-cell growth of reticular pattern from dog -	265
98	Basal-cell carcinoma of lip of dog - - - - -	266
99	Papillary carcinoma of third eyelid of horse - - -	267
100	Pigmented papilloma of groin - - - - -	269
101	Rodent carcinoma of back - - - - -	272
102	Satellite focus of basal-cell carcinoma - - - -	273
103	Superficial but non ulcerated cystic basal-cell growth of back -	273
104, 105	Superficial but non ulcerated cystic basal-cell growth of back of neck - - - -	274
106	Reticular structure of basal-cell carcinoma - - - -	275
107	Turban tumours in an old woman - - - - -	276
108	Solitary sub-epidermal mainly solid basal-cell growth from scalp -	277
109	<i>Detail of Fig. 108</i> - - - - -	278
110	Solid and cystic basal-cell growth of neck - - - -	279
111	Sub-epidermal cystic basal-cell growth of areola of nipple -	279
112	Solitary sub-epidermal cystic basal-cell growth of arm - - -	281
113	<i>Detail of Fig. 112</i> - - - - -	282
114	Rodent carcinoma of nose showing cornified foci - - -	283
115	Sweat glandular adenoma of finger - - - - -	284
116	Squamous metaplasia of sweat glands and ducts - - -	284
117, 118	Sweat glandular papilloma of surface of scalp - - -	285
119	<i>Detail of Figs. 117 and 118</i> - - - - -	286
120	Adenoma of tarsal gland - - - - -	287
121	Bowen's disease early lesion - - - - -	287
122	<i>Detail of Fig. 121</i> - - - - -	289

FIG		PAGE
123	Bowen's disease, later lesion - - - - -	290
124	Spinous cells in carcinoma of lip - - - - -	295
125	Diffuse spindle celled growth at invading edge of carcinoma of tongue	296
126	Metastasis of cornifying epidermoid carcinoma of the tongue in adrenal gland - - - - -	297
127	Carcinoma of lympho epithelial type probably arising in a branchial cyst - - - - -	305
128	Vertical section through a tooth germ of a 15 weeks foetus - - -	308
129	Horizontal sections through jaw of a 6 months foetus - - -	309
130	Adamantinoma - - - - -	312
131	Adamantinoma - - - - -	313
132	Adamantinoma - - - - -	314
133	134 Early squamous cell growth of subgingival epithelial residues -	316
135	A fibrotic area of parotid tissue on the outskirts of a tumour - -	325
136	Glandular tissue with epithelial sprouts passing into mucinous matrix simulating cartilage from a submaxillary tumour - - -	327
137	Solid epithelial clumps and columns with acinar cavities in places, and intervening mucoid matrix, in a parotid tumour - - -	328
138	Solid epithelial mass containing a spherule of eosinophil secretion in a salivary tumour - - - - -	328
139	Cribiform structure in parotid tumour - - - - -	329
140	Cornified "cell nests," along with some glandular structures, in a sublingual tumour - - - - -	330
141	"Adamantinoma" like structure with stellate celled epithelial reticulum in a parotid tumour - - - - -	331
142	Margin of a parotid tumour showing genesis of tumour - - -	331
143	Islands of residual parotid tissue deeply included in mucinous growth	332
144	A region of direction transformation of parotid acini into mucinous growth - - - - -	333
145	Neoplastic ducts and clusters of solid acini in a salivary tumour -	334
146	Recurrent infiltrating parotid tumour - - - - -	336
147	Metastatic spheroidal celled salivary tumour in a cervical lymph gland	339
148	Recurrent salivary tumour of cribiform structure infiltrating cervical fascia and platysma muscle - - - - -	340
149	Recurrent salivary tumour of undifferentiated carcinomatous structure	341
150	Metastasis of polyhedral and spindle celled salivary carcinoma in the adrenal gland - - - - -	342
151	Spindle celled sarcoma like structure of a metastasis of salivary carcinoma in the lung - - - - -	343
152	Whole section of adeno lymphoma - - - - -	344
153	Detail of Fig 152 - - - - -	345
154	155 Nasal adenocarcinoma - - - - -	350
156	Nasal mucoid adenocarcinoma - - - - -	351
157	Nasal 'papilloma' - - - - -	351
158	Details of nasal 'papilloma' - - - - -	352
159	Basal cell carcinoma ('adamantinoma') of antrum - - -	353, 354

LIST OF ILLUSTRATIONS

iv

FIG		PAGE
160	Adenocarcinoma of bronchus in a dog - - - - -	362
161	Spindle-celled carcinoma of bronchus - - - - -	367
162 163	Acinar and signet ring cell adenocarcinoma of lung - - -	368
164	Acinar and signet ring-cell adenocarcinoma of lung - - -	369
165	Metastasis of mucoid adenocarcinoma of lung in brain - - -	370
166	Metastasis of adenocarcinoma of lung in brain - - - - -	371
167	Metastasis of carcinoma of lung in a hydrocele - - - - -	375
168	Bronchial adenoma - - - - -	376
169	Bronchial adenoma details of structure - - - - -	377
170	Mucous glands included in bronchial adenoma - - - - -	378
171	Bronchial adenoma - - - - -	378
172	Bronchial adenoma like carcinoma of trachea - - - - -	379
173	Bronchial adenoma - - - - -	380
174	Bronchial adenoma - - - - -	381
175	Bronchial adenoma - - - - -	382
176	"Chondroma" of lung - - - - -	383
177	Carcinoma of oesophagus - - - - -	389
178	Glandular polypus of stomach - - - - -	396
179	Highly differentiated adenocarcinoma infiltrating gastric muscle - - -	402
180	Signet ring-cell mucoid carcinoma of stomach - - - - -	403
181	Pyloric carcinoma invading duodenum amidst Brunner's glands - - -	404
182	Krukenberg tumour of the ovary - - - - -	405
183	Signet ring-cell gastric carcinoma in lung - - - - -	405
184	Typical structure of argentaffin carcinoma - - - - -	414
185	Microscopic infiltration of outer coats of bowel by argentaffin carcinoma - - -	415
186	Typical structure of argentaffin carcinoma in a metastasis in the liver - - -	416
187 188	Anaplastic structure in argentaffin carcinoma - - - - -	417
189	Adenocarcinoma of colon in a rat - - - - -	420
190 191	Polyposis of colon - - - - -	422
192	Infiltration of muscular coat by argentaffin carcinoma of appendix - - -	427
193	Adenocarcinoma of anal canal - - - - -	428
194 195	Liver-cell tumours of dogs - - - - -	432
196	Liver-cell tumour of frog - - - - -	433
197	Liver-cell carcinoma in a case of haemochromatosis - - - - -	435
198	Multilocular cystadenoma of pancreas - - - - -	444
199 200	Adenocarcinomas of pancreas from cats - - - - -	445
201	Acinar type of adenocarcinoma of pancreas - - - - -	446
202	Metastatic mucoid adenocarcinoma of pancreas in lung - - - - -	447
203	Phagocytes accompanying the mucus produced by the tumour in the lung in Fig. 202 - - - - -	448
204	Metastatic adenocarcinoma of pancreas in a vertebra - - - - -	449
205	Microscopic infiltration of the meninges by metastatic adenocarcinoma of pancreas - - - - -	450
206	A small islet adenoma of the pancreas found at necropsy - - - - -	450
207	Adenoma of kidney papillary type - - - - -	451

FIG		PAGE
208	Adenoma of kidney, papillary type with granular calcification	454
209	Adenoma of kidney, collections of foam cells in the stroma	454
210	Adenoma of kidney, extension through fibrous capsule	455
211	Clear celled renal carcinoma, well differentiated tubules	458
212	Clear celled renal carcinoma, tubular and papillary structure	459
213	Clear celled carcinoma, primary growth in kidney	460
214	Clear celled renal carcinoma, trabecular pattern in a subcutaneous metastasis	460
215	A metastasis of renal carcinoma in the myocardium	461
216	Solid celled carcinoma of kidney	461
217	A prominent zone of fibrin at the margin of a metastasis of clear celled renal carcinoma in the brain	464
218	Metastasis of clear celled renal carcinoma in floor of mouth	464
219	Papillary carcinoma of ureter	468
220	Papillary carcinoma of bladder	469
221	Brunn's nests in chronic pyelitis	472
222	Well differentiated villous papilloma of bladder	473
223	Villous papillary carcinoma of bladder showing cellular pleomorphism	474
224	Pulmonary metastasis of carcinoma of bladder	475
225	Epidermoid carcinoma of renal pelvis	475
226	Umbilical tumour probably of urachal origin	479
227	Ovarian cortex of a phalanger	482
228	Intracystic fibro papillary growth of ovary	484
229	Pedunculated papillary growth in a unilocular ovarian cyst containing slightly mucinous fluid	485
230	From an hepatic metastasis of a solid spheroidal celled carcinoma of the ovary	488
231	A Walthard nest on the peritoneal surface of the Fallopian tube	490
232	Granulosa cell tumour of the broad ligament	493
233	Granulosa cell tumour of the ovary	494
234	Call Exner rosettes	495
235	Granulosa cell tumour of the ovary	495
236	Theca cell tumour of the ovary	496
237	Cystic granulosa cell tumour of ovary in a child	498
238	Mixed granulosa theca luteal cell tumour of ovary	499
239	Cystic endometrial hyperplasia accompanying theca cell tumour	500
240	'Arrhenoblastoma'	502
241	Dysgerminoma	506
242	Mesonephroma	508
243	Mesenophroma	509
244	Ovarian tumour from a dog, showing variations of structure	511
245	Ovarian tumour from a mare	512
246	Papillary adenocarcinoma of either tubal or ovarian origin	517
247	Papillary adenocarcinoma of the Fallopian tube	518
248	Peritoneal metastasis of Fallopian carcinoma	519

LIST OF ILLUSTRATIONS

vii

FIG		PAGE
249	Very early superficial epidermoid carcinoma of the cervix	325
250	Early epidermoid carcinoma arising in a cervical polypus	325
251	Great cellular and nuclear pleomorphism in epidermoid carcinoma of the cervix	325
252	Undifferentiated spindle celled clumps in a cervical epidermoid carcinoma	325
253	Rounded spaces in a very cellular rapidly growing epidermoid carcinoma of the cervix	325
254	Spread of epidermoid carcinoma of the cervix to the Fallopian tube	325
255	Solid clumps of a uterine adenocarcinoma occupying small veins	325
256	From a bulky endometrial carcinoma, showing the complex tubular pattern frequently seen in these growths	325
257	Islands of squamous epithelium in the glandular spaces of an endometrial adenocarcinoma	325
258	Pulmonary metastasis of uterine "adenomyoma"	325
259	Endometrial mixed tumour containing epithelium-lined spaces lined by cellular stromal tissue with abundant differentiated muscle	325
260	Early superficial carcinoma from near clitoris	325
261	Extensive superficial carcinoma of vulva	325
262	Section of vulval skin excised for leucoplakia showing characters of Bowen's disease	325
263	Detail of Fig 262	325
264	Cystadenoma of Bartholin's gland	325
265	Hydradenoma of vulva	325
266	Large lymphoid follicle in stroma of seminoma	325
267	Typical appearances of seminoma	325
268	Intra tubular growth of seminoma	325
269	Intra tubular multifocal seminoma	325
270	Intra tubular seminoma in 2 cases	325
271	Invasion of tunica albuginea by seminoma	325
272	Co-existent seminoma and teratoma	725
273	The seminoma in specimen	730
274	Co-existent seminoma and teratoma	730
275	Undifferentiated embryonic structures, from the teratoma	731
276	Undifferentiated embryonic structures, from the teratoma	732
277	Co-existent seminoma and teratoma	735
278	Seminoma and teratoma	737
279	Chorion and teratoma	741
280	Typical seminoma	742
281	Chorion and teratoma	743
282	Papillary chorion and teratoma	744
283	Multifocal chorion and teratoma	746
284	Interstitial chorion and teratoma	750

FIG		PAGE
285	Interstitial cell tumour with compressed clear celled structure from a dog - - - - -	581
286	Prostatic adenocarcinoma from a dog - - - - -	586
287	A metastasis of well differentiated prostatic adenocarcinoma in a cervical lymph gland - - - - -	587
288	Well differentiated prostatic adenocarcinoma - - - - -	588
289	Imperfectly differentiated prostatic adenocarcinoma - - - - -	588
290	Skilgram of two lumbar vertebrae containing osteoplastic metastases of prostatic carcinoma - - - - -	591
291	Osteoplastic vertebral metastasis of carcinoma of prostate - - - - -	592
292	Diagram to show distribution of spinal metastases in 4 cases of prostatic carcinoma - - - - -	593
293	Colloid adenoma of thyroid with much oedematous stroma - - - - -	602
294	So called foetal adenoma of thyroid - - - - -	603
295	Well differentiated colloid vesicular structure in a pulmonary metastasis of thyroid carcinoma - - - - -	605
296	From a lymph nodal metastasis of cystic papillary adenocarcinoma of thyroid - - - - -	605
297	Diffuse pleomorphic celled carcinoma of thyroid - - - - -	606
298	Large eosinophil celled (' Hurthle cell ') tumour of thyroid - - - - -	607
299	Carcinoma of lingual thyroid - - - - -	608
300	Cystic papillary adenocarcinoma of thyroid, metastatic in a lymph gland - - - - -	610
301	Mixed tumour of thyroid from a dog - - - - -	612
302	From pulmonary metastases of tumour shown in Fig 301 - - - - -	613
303	Diffuse thymic carcinoma with many admixed lymphocytes - - - - -	618
304	Cystic carcinoma of thymus - - - - -	619
305	Detail of Fig 304 - - - - -	620
306	Thymic tumour from a case of myasthenia gravis - - - - -	620
307	Detail of Fig 306 - - - - -	621
308	Pituitary adenoma composed entirely of eosinophil cells - - - - -	625
309	Anaplastic seminoma like malignant pituitary tumour - - - - -	627
310	Wall of a pituitary cyst lined by ciliated epithelium - - - - -	628
311	Pituitary 'adamantinoma' - - - - -	629
313	Cortical adenoma of adrenal gland - - - - -	632
314, 315	Parathyroid adenoma - - - - -	637
316	Parathyroid adenoma - - - - -	638
317	Chondrification in a subcutaneous fibroma - - - - -	648
318	Fibroma of the maxilla with calcified foci - - - - -	652
319	Myxosarcoma - - - - -	653
320	Nasal fibroma with focal calcification from a dog - - - - -	655
321 322	Congenital lipoma with included parotid glandular tissue - - - - -	659
323	Scrotal fibro lipoma - - - - -	661
324	Fibromatous area of scrotal fibro lipoma - - - - -	662
325	Mingled lipomatous and atypical fibromatous cells in a tumour of thigh - - - - -	663

FIG		PAGE
326	From a myxosarcomatous part of a large retroperitoneal lipoma	664
327	Benign osteoid tumour of skull from a child	673
328	Chondrosarcoma of humerus	676
329	Chondromatous osteoclastoma	683
330 331	Myeloid epulis	685
332	Osteosarcoma of broad ligament	688
333	From a lymph nodal metastasis of osteosarcoma of humerus in a dog	689
334	<i>Detail of Fig 333</i>	690
335	Fibromatous teno synovioma	695
336	Suprapatellar synovioma	696
337	Malignant teno synovioma of foot of pseudo-epithelial type	697
338	Malignant synovioma of knee of pseudo-epithelial type	698
339	Congenital angioma of dermis of shoulder	701
340	Plaque like angioma of skin of shoulder	701
341	Pedunculated angioma of skin of neck	704
342	A nerve bundle surrounded by and containing cavernous angiomatous channels	705
343, 344	Congenital angioma of muscle	706
345	Capillary angioma of cerebellum	707
346	Diffuse extensive angiomatosis of liver of a new born infant	709
347	Lymphangioma of epididymis	711
348	Glomangioma	714
349	Intra ventricular meningioma	720
350	Plaque like meningioma invading dura mater	721
351	Epithelioid structure in para sagittal meningioma	722
352	Epithelioid structure with small whorls in a meningioma	723
353	Whorled but non-calcified meningioma	723
354	<i>Detail of Fig 353</i>	724
355	Whorled fibrous meningioma with calcified spherules from thoracic part of the spinal theca	724
356	Ossified meningioma	725
357	Fat cells in a uterine myoma	730
358	Epithelioid appearances and hyaline change in a uterine myoma	730
359	Pulmonary metastasis of leiomyosarcoma	731
360	Pleomorphic celled part of uterine leiomyosarcoma	732
361	Well differentiated myomatous structure in hepatic metastasis of leiomyosarcoma of rectum	735
362	Retroperitoneal leiomyosarcoma	737
363	Rhabdomyosarcoma of middle ear region	741
364	Lingual 'myoblastoma'	742
365	Lingual myoblastoma	743
366	Cutaneous 'myoblastoma' of the knee region	744
367	Irregular overgrowth of the epithelium overlying a lingual 'myoblastoma'	746
368	Rhabdomyosarcoma of bladder	750

FIG		PAGE
369	Rhabdomyosarcoma of the prostate - - - - -	751
370	Large eosinophilic rhabdomyosarcoma cells in a mixed tumour of the endometrium - - - - -	753
371	Follicular lymphosarcoma - - - - -	764
372	Lymphosarcoma invading lung - - - - -	766
373	Hyaline trabeculae in lymphosarcoma - - - - -	767
374	Large undifferentiated cells, resembling those of Hodgkin's disease, in lymphosarcoma - - - - -	767
375	Inginal gland from a case of generalized lymphosarcomatosis - - - - -	768
376	From same tumour as Fig 375, showing undifferentiated syncytial type of growth - - - - -	769
377	Cortical zone of a cervical lymph gland affected by early Hodgkin's disease - - - - -	772
378	Detail of Fig 377 - - - - -	773
379	Reticulosarcoma of epitrochlear lymph gland - - - - -	778
380	Diffuse fibrosing reticulosarcoma with admixed lymphocytes - - - - -	779
381	Smear of myeloma plasma cells - - - - -	785
382	Section of solitary plasmocytoma of vertebra - - - - -	789
383, 384	Lung from patient with severe myelogenous leukaemia - - - - -	793
385	Testis from patient showing severe myelogenous leukaemic infiltration - - - - -	794
386	Mitoses in a blood film from a case of myelogenous leukaemia - - - - -	795
387, 388	Malignant erythroblastoma - - - - -	798
389	The liver from same case as Figs 387 and 388 - - - - -	799
390	Basophil cell tumour from a dog - - - - -	800
391	Well differentiated astrocytoma of cerebrum - - - - -	808
392	Highly differentiated fibrous astrocytoma of pons - - - - -	809
393	A well differentiated fibrous astrocytic area in a cellular "glioblastoma" of cerebrum - - - - -	810
394	Tumour astrocytes in a cellular glioma of cerebrum - - - - -	810
395	Well differentiated fibrillary area in a cellular astrocytoma of cerebrum - - - - -	811
396	Fusiform celled fibrillary area in the same tumour as Fig 395 - - - - -	811
397	Pleomorphic celled anaplastic astrocytic glioma of cerebrum (glioblastoma multiforme) with many large cells - - - - -	812
398	Cellular glioma of fourth ventricle showing perivascular arrangement of cells - - - - -	812
399	Astrocytic glioma of cerebrum showing perivascular arrangement of cells - - - - -	813
400	Oligodendroglioma of cerebrum - - - - -	814
401	Rosettes in a medulloblastoma of cerebellum - - - - -	816
402	Diffuse spread of medulloblastoma in meninges - - - - -	816
403	Peculiar cellular glioma of cerebrum probably medulloblastoma - - - - -	817
404	Primary papillary growth of choroid plexus - - - - -	825
405	Metastasis of choroid plexus tumour on surface of spinal cord - - - - -	825
406	Neurilemmoma of tongue - - - - -	829
407	Neurilemmoma of parotid gland - - - - -	830
408	Neurilemmoma of medulla of adrenal gland - - - - -	830

FIG		PAGE
409	From the same specimen as Fig 408 showing two nerve cells included within the whorled regimented tumour tissue - - - -	831
410	Subcutaneous neurilemmoma of the back - - - -	831
411	<i>Detail of Fig 410</i> - - - -	832
412	Intrathecal neurilemmoma - - - -	833
413	Malignant neurilemmoma of abdominal wall - - - -	835
414	Neurofibromatous thickening of dermis including a nerve with great thickening of its sheath - - - -	836
415	Neurofibroma of small intestine, with included nerve cells of Auerbach's plexus - - - -	837
416	Coeliac ganglion of 4 months human foetus showing neuroblastic rosettes - - - -	845
417	From pulmonary metastases of a primary neuroblastoma of the coeliac ganglion - - - -	848
418	<i>Detail of neuroblastic rosettes from the same tumour as Fig 417</i> - -	849
419	A group of nerve cells in a ganglioneuroma of thoracic sympathetic chain - - - -	850
420	Well differentiated part of retroperitoneal ganglioneuroma - -	857
421	Drawings of individual cells from same section as Fig 420 - -	858
422	Neuraxons in ganglioneuroma selectively stained by Cajal's pyridine silver method - - - -	859
423	Rosettes with fibrils in neuroblastomatous part of same tumour as previous Figs - - - -	859
424	Skiagram of piece of skull showing spines of new bone formed in metastatic neuroblastoma - - - -	860
425	Areas of imperfectly differentiated ganglioneuromatous cells and bundles of non medullated nerve fibres - - - -	860
426	<i>Detail of Fig 425</i> - - - -	861
427	Well differentiated nerve bundles with abundant Schwann cells in ganglioneuroma - - - -	862
428	Skiagram of femur showing onion skin layers of new bone evoked by metastatic neuroblastoma - - - -	865
429	Rosettes in primary adrenal neuroblastoma - - - -	865
430	Skiagrams of fusiform fibular tumour showing onion skin layers -	867
431	Carotid body tumour showing groups of epithelium like cells separated by vascular spaces - - - -	874
432	<i>Detail of cells of the same tumour as Fig 431</i> - - - -	875
433	Section of 8 mm human embryo showing early optic cup in continuity with floor of brain - - - -	878
434	Section of optic cup of 12.5 mm human embryo - - - -	878
435	Section of optic cup and stalk of 28 mm human embryo showing early stratification of retina proper and dense pigmentation of outer layer of cup - - - -	879
436	Section of detached retina showing outer nuclear layer limiting membrane and swollen rods and cones projecting into sub retinal space - - - -	880
437	Retinoblastoma showing areas of rosetted and fibrillar tumour - -	884

LIST OF ILLUSTRATIONS

	PAGE
Detail of fibrillar area of Fig 437	885
Retinoblastoma rosettes	887
Eye showing retinal detachment with retinoblastoma	890
Eye with retinoblastoma showing spread of growth to ciliary body and iris and over front of lens	891
Cross sections of optic nerves invaded by retinoblastoma	892
Pigmented mole of arm showing papillary structure frayed epidermis and masses of naevus cells	900
Detail of Fig 443, showing identity of frayed epidermal and naevus cells	901
Papillary pigmented mole showing clusters of naevus cells detached from epidermis	902
Detached clumps of naevus cells in dermal papillae, and deeply pigmented epidermis	902
Neurofibromatoid tissue beneath a pigmented mole	903
Amelanotic melanoma	907
Amelanotic part of recurrent melanoma	908
Metastatic round celled melanoma in inguinal lymph gland	909
Metastatic melanoma of brain	909
Normal meningeal pigment cells in a strip of pia mater	913
Melanoma of brain	914
Large multinucleated chordoma cells with many intracellular vacuoles	920
Typical chordoma	921
Nephroblastoma	926
Nephroblastoma	927
Nephroblastoma	928
Pro glomerulus in nephroblastoma	928
Papillary growth of nephroblastoma into renal pelvis showing orderly clothing of tumour by pelvic epithelium	929
<i>Detail of Fig 460</i>	930
Embryonic hepatoma	934
Liver of a 2.7 centimetres human embryo	935
Drawing of benign teratoma of ovary	944
Diagram of tissues found in vertical section of tumour shown in Fig 464	945
Slice of an ovarian teratoma composed of a solid and polycystic mass projecting into a large thin walled cyst	946
Diagram of structure of a slice of large retroperitoneal teratoma	949
Intra pericardial teratoma	951
Ciliated respiratory epithelium in a teratoma	956
Gastric mucosa in a teratoma	957
Pancreatic tissue with islets of Langerhans in a teratoma	957
Lung tissue in a teratoma	958
Embryonic neuro epithelial plaques and tubules in a teratoma	958
Small cavity in a teratoma lined partly by embryonic nervous tissue and partly by deeply pigmented ocular epithelium	959
Embryonic renal tissue in a retroperitoneal teratoma	960

uncommon in individual tumours of this kind the majority of myomas grow progressively and often to a huge size. The individual myoma which exhausts its power of growth during the lifetime of the body in which it lives is not thereby to be placed in a different class from all the other progressively growing myomas. In rare cases even malignant tumours have been known to become quiescent or even to disappear. This, however, does not invalidate the all too general rule that untreated malignant tumours grow progressively to a fatal termination and the occasional exceptional tumour is none the less a tumour of the same class as its fellows.

The most distinctive characteristic of a neoplasm is that it retains its property of persistent excessive growth independently of the stimuli which evoked it. There is ample evidence of this, in spite of the defects in our knowledge of the causation of many kinds of tumours. The experimental evidence alone is conclusive. Experimentally produced tumours of every kind may develop long after applications of the chemical or physical carcinogens have been discontinued, and the growth of established tumours proceeds indefinitely without further applications of the carcinogens. This irreversible neoplastic habit of growth, not dependent on the continued presence of the evoking agent, is most strikingly apparent with transplantable tumours, for these can be transferred by successive passages to many other animals and yet retain their neoplastic properties unimpaired. Cultures of tumour cells *in vitro* also maintain their peculiar properties and grow into tumours when engrafted into fresh hosts.

So also with human tumours, of those the extrinsic causative agents of which are known many develop long after these agents have ceased to act. Mule spinner's cancer, lung cancer in the Schneeberg miner, retinic cancers of the fair skinned farmer or sailor—these may all appear many years after the victims have retired from their hazardous occupations. Of course there are many patients who are still engaged in these occupations at the time when their tumours first appear, but such continuous exposure to carcinogenic stimuli is clearly not essential for the initiation of tumours, much less for their continued growth once they have developed.

It may be objected that there is no proof that during the genesis and subsequent growth of a tumour the responsible carcinogen has ceased to act, but that, for example, a carcinogenic hydrocarbon may be retained in infinitesimal but effective amounts in the cells of the established tumour evoked by it. A little reflection, however, will show the untenability of this view. We know from experiments (see Chapter 4) that extremely minute quantities of chemical carcinogens, e.g. 0.0004 milligram of dibenzanthracene, can evoke transplantable tumours. To suppose that such minute quantities are retained in the tissues to be distributed indefinitely amongst all the cells of the growing tumour, its metastases and its transplants is to suppose the impossible: there would not be enough molecules of the substance to permit of such unlimited distribution. Again the genesis and growth of tumours evoked by ultra violet light, X rays or other radiations are clearly not dependent on continued applications of rays: the retinic or X ray cancer may appear and progress long after exposure has ceased. It might be argued that the radiations act only indirectly by producing a chemical carcinogen

in the tissues and that it is this which persists in and maintains the growth of the resulting tumour, but this, of course, is the same impossible supposition as we have just rejected.

It is clear that tumour growth cannot be conceived as being maintained by the continued stimulation of the tumour tissue by the same agents as evoked it. These agents must act by initially inducing in the cells irreversible changes of metabolism and proliferation, which are then transmitted indefinitely to the descendants of the initially changed cells—in the primary tumour, in its metastases, in transplants and in explants *in vitro*. The nature of these changes, the very essence of the neoplastic reaction, is still unknown, it is discussed further in Chapter 11.

DEFECTS OF SOME PREVIOUS DEFINITIONS

Some previous definitions of tumour have failed in that they have omitted the all important characteristic of continued disproportionate growth independent of evoking stimuli. Thus Powell White's definition adopted by both Adams and Kettle, defined a tumour as a 'mass of cells, tissues or organs, resembling those normally present in the body, but arranged atypically, which grow at the expense of the organism without, at the same time, subserving any useful purpose therein'. Because this definition said nothing of a tumour's progressive disproportionate growth, it failed to distinguish tumours from malformations to all of which it was perfectly applicable. Failure to make this distinction has led to the unwarranted inclusion of a number of simple malformations amongst tumours—an error which is discussed further below.

The unlimited disproportionate growth of tumours has led many writers to infer erroneously that tumours possess complete autonomy and are exempt from the laws of normal growth. Thus MacCallum's definition includes the statement that tumours 'grow without any regard for the laws which govern and restrain the growth of normal tissues' and it has often been asserted that tumours 'grow without control' in an anarchic manner, 'lawlessly' or 'as parasites'. Ewing defines a tumour as "an autonomous new growth of tissue". But as Nicholson (1921) so emphatically insisted and as Foulds (1940) has more recently repeated the orderly architecture and functional activity of many tumours refute such views. Again Nicholson (1933) pertinently said, "It is all very well to prate of the laws of normal growth which are 'transgressed' by autonomous tumours. But it would be better still to enumerate these laws, to show how they are enforced in normality and in morbid states in which there is no autonomy of the peccant part, and above all to decide on the guilty party when they are broken. Tumours are neither 'lawless' nor autonomous in the sense that they obey peculiar laws of their own. The idea that tumours are "lawless", "anarchic" or "parasitic" clearly arises from too exclusive a view of the malignant tumours of rapid growth, poor cellular differentiation and destructive effects. These malignant qualities obtain in only a proportion of tumours and then in very variable degrees. The terms 'autonomy' or 'lawlessness' as applied to tumours are indeed but figurative ways of expressing their main characteristic, namely, their continued excessive cellular

proliferation, not dependent on continuance of the initial carcinogenic stimulus. It is this only that constitutes their 'anarchy'.

HOW TUMOURS DIFFER FROM OTHER PROLIFERATIVE LESIONS

To clarify still further our concept of a true tumour it will be helpful to state briefly how tumours differ from (1) inflammatory and reparative proliferations, (2) hyperplasias, and (3) malformations with excess of tissue.

(1) How tumours differ from inflammatory and reparative proliferations

Reparative proliferation of cells either in purely reparative processes or in association with inflammatory changes clearly has a useful function namely repair. This is most evident in simple healing lesions such as a clean granulating wound or a uniting fracture but in chronic inflammatory lesions also like those of tuberculosis or syphilis the newly formed tissue though frustrated in its reparative function and itself damaged by the persisting microbe is still of reparative value for if the parasite is eliminated this tissue promptly completes the healing of the lesion. It may be remarked in parenthesis here that to say that inflammation and repair are functionally 'useful' does not commit us to any narrow teleological view any more than to say that the function of the liver in secreting bile is 'useful'. All that is implied in these statements is that the processes in question contribute to the preservation and health of the organism. In this sense reparative proliferation has value, while neoplastic proliferation has not. The cellular multiplication of reparative tissues unlike that of tumours is not progressive and continuous but is limited by the extent of the breach to be filled or the duration of the tissue damage evoking it.

(2) How tumours differ from hyperplasia

The usual definition of hyperplasia as 'an abnormal increase in the cells of a tissue' (as in Webster's dictionary or Gould's medical dictionary) is too broad to be useful: it includes for example all tumours. If the term is to have value in pathology its meaning must be restricted and clearly specified as follows. Hyperplasia is the proliferation of the cells of a tissue either (a) as a compensatory response to loss of tissue of the same kind or to increased functional demands which the normal amount of tissue cannot satisfy, or (b) as a result of disturbed hormonal control of the activity of the tissue.

Examples will make these meanings clear. If liver tissue is lost either by excision or by damage by poisons new liver cells are freely produced by mitotic proliferation from surviving liver tissue. Similarly loss of kidney tissue by removal or disease is followed by increase in bulk of the remaining renal tissue by proliferation of the epithelial cells of surviving tubules. Removal of part of an endocrine gland is commonly followed by proliferation of the cells of the remainder so that the normal amount of the tissue is almost or quite restored. In anaemias increased erythropoiesis is seen in the hyperplastic red bone marrow, while in inflammatory diseases with leucocytosis the leucopoietic cells of bone marrow show hyperplasia. Compensatory hyperplasias are allied to repair from which however they differ in the specificity of the regenerated cells and in the fact that the regeneration is not restricted to the immediate site of tissue

loss The function of repair is to fill a breach, the function of regenerative hyperplasia is to compensate for the loss of cells of a specific kind

The second type of hyperplasia, that due to disturbed hormonal activity, is exemplified in the ductless glands themselves and in organs whose functions and structure are under hormonal control, such as the breast, uterus and prostate. These hyperplasias include such familiar lesions as goitres, cystic and lobular mastopathy, various endometrial overgrowths including endometriosis, and benign prostatomegaly. In some of these the nature of the responsible endocrine disturbance is known, in others it is still obscure.

Hyperplasias of both kinds differ from tumours in that the proliferation is limited in amount and duration, it progresses only so long as the functional need or hormonal stimulus which evoked it persists. Hyperplasias of the regenerative or compensatory type also of course differ radically from tumours in possessing functional value, this is their very *raison d'être*.

That neoplasia may supervene on hyperplasia a subject to be discussed in Chapter 7 does not invalidate, but serves rather to emphasize, the distinction between the two. If in a hyperplastic tissue, proliferation becomes excessive and independent of persistence of the stimulus which induced it then we recognize that a new quality in the proliferation, that of neoplasia, has supervened.

(3) How tumours differ from malformation with excess of tissue

By a malformation I mean an anatomical error arising in the course of development of the body to its adult state. As might be expected, the embryonic stages of development, when the greatest structural changes are in progress, are the most productive of developmental errors, more so than the later foetal or infantile stages, when architectural moulding is less in evidence than growth in size (see Ballantyne, 1902). Hence most malformations are congenital, they have arisen from disturbances of embryonic or foetal development. Many of these are already clinically apparent at birth, others do not make their clinical appearance until later but are nevertheless present in inconspicuous form at birth.

It is, however, a mistake to assume that all malformations are congenital, for quite apart from mere growth in size, the developmental modelling of organs and the differentiation of tissues are not complete at birth. A child is not a tiny adult, many of its parts are still immature and in process of genesis. Thus adult structure is clearly not attained in the genital system until after puberty, in the skeleton until the epiphyses are united, in the jaws until the permanent teeth are erupted, and, microscopically, complete differentiation of renal tissue, sympathetic ganglia and some endocrine tissues is not attained until some years after birth. The structural immaturity of many parts in childhood and adolescence is as it were, a projection of embryonic and foetal development into postnatal life, and in such parts minor malformations theoretically may and in fact do, sometimes arise from disturbances of postnatal development.

While the term 'malformation' thus legitimately includes not only errors of development present at birth but also those due to disturbances of the postnatal development of tissues still immature its meaning should not be extended to embrace anomalies of structure acquired after adulthood of the affected tissues has been attained. It is true that our tissues and organs change throughout life,

and that in this sense development continues until death, but in the more usefully restricted sense, development of a part is complete when it is fully formed or shaped to the adult pattern. After this although it may vary in size and structure for functional or nutritional reasons and although it may suffer various kinds of injuries to which it may react in various ways, it can no longer suffer developmental malformation in the usefully restricted sense of that term. Lesions acquired after attainment of the adult state of a part represent disturbances, not of development but of maintenance, they are deformations not malformations. I cannot subscribe to Nicholson's view (1921 and 1926) that tumours generally can be looked upon as malformations.

Malformations which involve no excess of tissue such as absence or deficiency of parts, and arrest of development such as cleft palate or imperforate anus, of course cannot be mistaken for tumours. Even many malformations with excess of tissue such as supernumerary or giant digits, accessory spleens or duplicated ureters, cannot be confused with tumours. Such confusion has occurred most frequently as regards those malformations in which the various tissues of a part are present in improper proportions or distribution with prominent excess of one particular tissue. Such tumour-like malformations, designated by Albrecht (1904) "hamartomas", include most angiomas, benign pigmented moles, most of the neurofibromatous masses of von Recklinghausen's disease and the cartilage-capped multiple exostoses. All of these will be discussed in due course. Here the common angioma or birth mark will serve as an example.

That the ordinary cutaneous angioma, such as the 'port wine stain', is a malformation and not a tumour will be clear from the following facts. It is present at birth, it grows only with the growth of the rest of the body, and does not extend to involve a greater and greater territory of tissue. After growth ceases it usually remains unchanged for the remainder of life unless accidents such as trauma, thrombosis, haemorrhage or infection take place in it. Briefly, it has no disproportionate or progressive powers of growth. Further, no sharp distinction can be drawn between the commoner varieties of angioma and the rarer plexiform or racemose angiomas, 'cirsoid aneurysms', and widespread 'angiomatoid dilatation' of the vessels of the central nervous system or elsewhere, and these rarer forms are clearly only vascular malformations.

The growth of a malformation differs fundamentally from that of a tumour in that it is limited and co-ordinated with that of the rest of the body. The ordinary angioma enlarges only *pari passu* with the part of which it is a blemish; then stops, it does not extend beyond the territory originally involved. A pigmented mole, though it displays a stage of youthful development, remains restricted to its particular field of origin and usually exhibits later retrogressive senescent changes. The growth of cartilage-capped exostoses ceases when the cartilage undergoes complete ossification about the period of union of the epiphyses. In short, malformations have no powers of excessive uncoordinated growth.

Finally, however, it must be noted that there are certain tumours which are also malformations, the teratomas and the true embryonic tumours. While these are clearly neoplasms, often malignant neoplasms, they also conform to our strict definition of malformations as anatomical errors arising in the course of the body to its adult state. They are disturbances of development of immature

tissues involving their neoplastic conversion, and there is little doubt that this is due, not to the application of any extraneous carcinogenic substance, but to disordered chemistry in the tissues themselves during their embryonic growth. Aetiologically as well as structurally, then, these neoplastic malformations differ from the much commoner tumours acquired in later life.

CONCLUSION

The most distinctive character of neoplastic proliferation is that it is unco-ordinated independent of the structural and functional pattern of the organism, and indefinitely progressive. In this, it differs fundamentally from reparative growth, hyperplastic growth and the growth of malformations in all of which the cellular multiplication is limited in amount and duration in accordance with more or less clearly specifiable factors. It is clear that neoplasia involves some permanent cellular change manifesting itself in excessive multiplication, that this change is transmitted to the descendants of the first affected cells to an indefinite number of generations and that it persists in these without continuance of the stimuli which initially evoked it.

REFERENCES

- Adam G (1909) *Principles of Pathology* London
 Albrecht P (1904) *Verh Dtsch path Ges* 7 153
 Ballantyne J W (1902) *Manual of Antenatal Pathology and Hygiene* Vol I p 79 Edinburgh
 Ewing J (1940) *Neoplastic Diseases* p 9 Philadelphia
 FOULDS L (1940) *Amer J Cancer* 39 1 (A valuable and provocative summary of our knowledge of many aspects of the structure and properties of tumours)
 Kettle E H (1925) *The Pathology of Tumours* London
 MacCallum W G (1940) *A Textbook of Pathology* p 1047 Philadelphia
 NICHOLSON G W (1921 1922 and 1933) Studies on Tumour Formation Nos I IV and XII *Guy's Hospital Reports* (These and Nicholson's other studies are invaluable to the student of tumour pathology. Not only are they a mine of information and personal observations illustrated by the most admirable photomicrographic drawings by Nicholson himself but also by their critical outspokenness, their humour and irony and their philosophical and classical flavour they make delightful and stimulating reading. They will be referred to frequently in this book.)
 NICHOLSON, G W (1926) *The Nature of Tumour Formation* (Erasmus Wilson Lectures 1925) Cambridge (A valuable supplement to his foregoing studies)
 Willis R A (1934) *The Spread of Tumours in the Human Body* p 105 London

CHAPTER 2

CLASSIFICATION AND NOMENCLATURE

THE OBJECT of any classification is to arrange a collection of diverse things into named groups and subgroups of similar or related individuals. The individuals composing a group are not usually replicas of each other, but they resemble one another more closely than they resemble those of other groups. Such a system is convenient indeed an indispensable aid to thought but its inherent limitations must be clearly recognized. Especially in biological subjects sharp separation of groups of individuals is not possible. the different classes which we create and name though convenient are not distinct in any absolute sense. Just as the systematic botanist or zoologist recognizes that living creatures in each group show such a range of variation that the boundary lines between related genera and species and between species and varieties are often difficult to define so also the pathologist must recognize similar intrinsic difficulties in the classification of tumours. The individual tumours of each main group exhibit a great range of structure and behaviour so that sub divisions within the group like those of species within a genus, are largely arbitrary. Unfortunately here as in other fields of thought once we have given a name to such an arbitrarily determined group we are apt to forget its arbitrary character and to accept the name as denoting a specific entity. Further some names in current use perpetuate erroneous hypotheses regarding the origin and nature of certain tumours. Perhaps pathology more than most branches of biological science suffers from this tyranny of names.

In framing our classification and terminology of tumours then we should be guided by the following two rules

(a) Our grouping should be simple and basic avoiding as far as possible the creation of artificial arbitrary sub divisions

(b) Our nomenclature should be simple and precise excluding all names of erroneous or doubtful meaning or where common usage necessitates their retention for the time being indicating their defects and suggesting preferable substitutes

The multiplication of new names should be avoided in my opinion the familiar terminology in current use affords enough suitable names for our purposes, the meaning of each name employed however must be made precise and clear

HISTOGENETIC CLASSIFICATION

Unquestionably the fundamental basis of scientific classification is histogenetic that is according to the tissues from which tumours arise and of which they consist. As we have already noted in Chapter 1 the essential parenchyma of a tumour consists in most cases of cells of a single type derived from one only of the tissues of the body clearly the tumour should be named and classified according to the nature of this tissue. As Mallory insisted Tumours are classified like normal tissues on a histologic basis. The type of cell is the one

important element in every tumor. From it the tumor should be named, not from some peculiarity of minor importance, such as method of growth or arrangement of cells, or form of retrograde change.

Microscopical identification of the nature of a tumour depends on the recognition of the kind of cells composing it. When the cells are well differentiated, as they often are in slowly growing tumours, a microscopical diagnosis of the nature of the tumour is usually easy. When growth is rapid, however, cellular differentiation may be very imperfect or entirely wanting and microscopical identification of the specific nature of the tumour may then be difficult or impossible. With increasing experience the histopathologist learns to recognize those slight degrees of differentiation in tumour tissues which elude the beginner. Sometimes also an otherwise undifferentiated tumour may contain scanty areas with sufficient differentiation to permit specific diagnosis, but prolonged search may be necessary to find these.

The following example will serve to illustrate the variable degree of differentiation, and therefore of specific histological identification, possible in tumours all of the same origin. A carcinoma of the thyroid may, in parts, present almost perfect differentiation of unmistakable thyroid vesicles filled with colloid secretion, so that from histological study alone a confident diagnosis of "adenocarcinoma of thyroid tissue" can be made. Sections of a second thyroid carcinoma may exhibit well marked glandular architecture but without the formation of recognizable thyroid vesicles or colloid, so that the histologist can identify the growth as "adenocarcinoma", but cannot assert its thyroid origin. Sections from a third carcinoma of the thyroid may display clear evidence of its epithelial nature in the grouping of its cells in circumscribed compact clumps but may be devoid of any glandular orientation of the cells, the tumour can then be identified no more specifically than "carcinoma". Finally, a fourth tumour may be so lacking in differentiation that even the epithelial nature of its cells cannot be inferred from its structure or arrangement, the histologist alone can identify it then only as "a highly cellular anaplastic tumour of undetermined origin". Thus, while all four tumours are of the same kind, namely "carcinoma of the thyroid", the precision of histological identification which is possible varies from tumour to tumour, and this is reflected in nomenclature. It may be noted here that a single tumour may display in different parts all these varieties of structure so that the degree of precision of the histological diagnosis will depend on the part of the tumour examined, a point which is often overlooked in attempts to assess the relative malignancies of different tumours in one class.

There occur tumours corresponding to almost all kinds of normal tissues, and clearly our classification of tumours will run parallel with our classification of normal tissues. Just as the histologist may conveniently group these tissues into several main classes—such as epithelia of various types, non epithelial (connective, vascular, skeletal, muscular and haemopoietic) tissues, nervous tissues, etc.—so the pathologist may group tumours into corresponding main classes. In a general way the prevailing nomenclature of tumours, although defective in some respects, has followed this course.

The histogenetic classification of tumours encounters difficulties of two kinds: (a) those due to lack of precision in the histological classification and naming of normal tissues, and (b) those due to uncertainty regarding the tissues of origin.

of some kinds of tumours. Difficulties of the former kind must be resolved by the anatomist and embryologist and of the latter kind by the pathologist.

(a) Lack of precision in histological nomenclature is well exemplified in the usage of the familiar name *epithelium*. While everyone agrees that this properly applies to the epidermis, the lining cells of visceral mucous membranes of all kinds, and the secreting cells of glandular derivatives of these, whether exocrine or endocrine, there is still disagreement as to whether the cells lining the serous and vascular cavities should be called *epithelium*. That these cells have little in common with those of the epidermis and visceral linings has been recognized by both anatomists and pathologists. As long ago as 1865 His proposed to distinguish the false from the true *epithelium* by calling the former *endothelium* and later Minot suggested that the term *mesothelium* should be used to distinguish the coelomic cells from the vascular endothelium. While this practice has been followed by many histologists (e.g. Bremer and Weatherford, Maximow and Bloom), most pathologists continue to call both coelomic and vascular linings *endothelium*. Again while all agree in applying the term *epithelium* to the parenchyma of those endocrine glands which develop as outgrowths from epithelial surfaces, namely the anterior part of the pituitary, the thyroid, parathyroid and islets of Langerhans, histologists are reluctant to call the adrenal cortex or the interstitial cells of the testis by this name. Neither Maximow and Bloom nor Bremer and Weatherford use the word *epithelium* in their descriptions of the adrenal cortex, though the latter refer to the *epithelioid* cells and Maximow and Bloom speak of the interstitial cells of the testis as *epithelioid*. There is room for doubt as to the propriety of speaking of ependyma as an *epithelium*, and some histologists might even disagree with Bremer and Weatherford in referring to the cells of the pineal glands as *epithelioid*. These uncertainties in histological nomenclature have been reflected in pathology, e.g. tumours supposed to have arisen from coelomic lining cells have been called 'carcinoma', 'endothelioma', 'mesothelioma' and 'serosal epithelioma' (see Kaufmann, 1929). The difficulty of classifying many thymic tumours has led to wide use of the non-committal name *thymoma* and most pathologists have preferred to speak of '*interstitial cell tumours of the testis*' rather than to designate them as 'adenomas' or 'carcinomas'. On the other hand it is usual to refer to adrenal cortical tumours as 'adenomas' and 'carcinomas', thus implying an epithelial character which, as we have seen, many histologists frankly do not endorse. These and other difficulties arising out of purely histological considerations will be dealt with each in its appropriate place in this work.

(b) The second difficulty in histogenetic classification, namely that due to uncertainty regarding the precise tissue of origin of some kinds of tumours, is not a very serious one. It now obtains with only a few kinds of tumours and these will certainly diminish in number as histopathological research advances. The ovary remains the most perplexing region as regards the derivation of many of its tumours, partly because of the great variety of tumours observed in this organ, not a few of which consist of tissues not recognizably like any of the normal constituents of the ovary, and partly because of uncertainty regarding the histogenetic relationships of normal tissues in the ovary in which it now appears probable stromal and epithelial elements may be interchangeable. The teratomas

comprise another group of neoplasms of undetermined histogenesis, but recent progress in experimental embryology and in the study of teratomas promises to discover ere long the nature and mode of origin of these growths

Criticisms of the histogenetic basis of tumour classification such as MacCallum's (1940), are groundless. MacCallum wrote, 'Classification is at best unsatisfactory on a histogenetic basis since so often we cannot make a good guess at the tissue which the tumor most resembles or the point from which it actually springs'. Such a statement from an experienced pathologist is incomprehensible. On the contrary, the evidence for the origin of tumours from their specific normal counterparts is for most classes of neoplasms, precise and conclusive. 'good guesses' are unnecessary. It is true that there remain some small groups of tumours the tissues of origin of which are still uncertain. As we have seen, it is also true that some individual tumours in any of the main groups of neoplasms are so anaplastic that histological recognition of their identity is not possible. But neither of these is a valid reason for denying histogenesis as the obvious and essential basis of tumour classification. MacCallum was moreover inconsistent for his arrangement of tumours into twelve groups was basically histogenetic. He insisted that this was 'an arrangement, not a classification', but what is a 'classification' if it is not an 'arrangement'?

BEHAVIOURISTIC CLASSIFICATION INNOCENCE AND MALIGNANCY

In addition to the fundamental histogenetic classification by which tumours are grouped solely according to the kinds of tissue from which they spring and of which they consist, it is also necessary to have a further grouping biologically less fundamental but of great practical value, according to their behaviour and clinical progress.

The tumours of any given cell type may show a wide range of behaviour in their rates of growth, powers and modes of spread and degree of danger to their victims. Some grow only slowly, remain quite local, do not invade neighbouring tissues, and cause no harm except by virtue of their position or some accidental complication; these are *benign* or *innocent* tumours. Other tumours of the same cell type grow rapidly, invade neighbouring tissues, spread by metastasis and, unless extirpated at an early stage, inevitably prove fatal: these are *malignant* tumours. Between these two extremes however, many of the histogenetic groups contain tumours of intermediate or borderland behaviour, so that sharp division into innocent and malignant species is not possible. 'Innocence' and 'malignancy' are relative terms used to make a convenient but arbitrary separation of members of any particular histogenetic series into two sections according to those biological characters which are of greatest significance for prognosis. This subject is discussed at greater length in the next chapter.

Some writers notably Muir (1941) while appreciating the importance of histogenesis have unduly stressed the distinction between innocence and malignancy by making it the primary step in their classification. Thus Muir adopts the primary division of tumours into innocent "Histiomata or tissue tumours" and malignant "Cytomata or cellular tumours". This plan is unfortunate, it over emphasizes the behaviouristic basis of classification by the use of two misleading and unnecessary names. To call a tumour a 'cytoma' rather than a

"histioma" is in effect to say that it consists of cells but not of tissue, a statement which save for its possible application to the extremest instances of anaplasia, is clearly false. Muir presumably does not intend this literal meaning to be attached to the terms although he specifically translates them as meaning 'tissue tumours' and 'cellular tumours' respectively. The intention is to express in terminology the fact that innocent tumours usually exhibit a high degree of histological differentiation and so resemble the corresponding normal tissues, while malignant tumours often show anaplasia of various degrees. But there are better ways of expressing this than by introducing two questionable words as the very basis of classification, and moreover, many malignant tumours are highly organized.

While no fundamental distinction can be made between innocent and malignant tumours the distinction for practical prognostic purposes can be made microscopically in the majority of cases. This applies particularly to some of the commonest groups of tumours, notably to most epithelial and to many tumours of the non epithelial mesodermal tissues. Thus there is usually no histological difficulty in pronouncing a tumour of glandular origin to be either a benign adenoma or a malignant carcinoma or in distinguishing an innocent lipoma, osteoma, or leiomyoma from the corresponding malignant sarcoma. However, papillary epithelial tumours not infrequently exhibit borderline behaviour and so render histological prognosis difficult and the same applies to some fibromatous and chondromatous tumours. As regards the tumours of neural tissues, especially the common gliomas, sub division into 'innocent' and 'malignant' classes is quite arbitrary and serves no useful purpose for these tumours show all possible gradations between slowly growing well differentiated types and rapidly growing anaplastic types and even the former are infiltrative in their mode of growth. Some other groups of tumours, e.g. melanoma, chordoma, chorion epithelioma and embryonic tumours of viscera are always to some degree malignant and have no really benign counterparts so that behaviourist sub division of these groups is not called for.

IMPROPER BASES OF CLASSIFICATION

It is necessary to consider here in order to discard certain other bases which have been used in classifying tumours. These are (1) regional, (2) embryological, (3) aetiological.

(1) Regional classification

To a certain degree histogenetic classification is of course regional. Gliomas can arise only in the central nervous system, myelomas only in bones, chordomas only in the spinal axis and so on. Again innocent epithelial growths often possess such distinctive histological structure that this alone permits identification of their specific regional origin, e.g. papillomas of the urinary tract or of the large intestine or adenomas of the breast or thyroid. Even some carcinomas possess a microscopical structure pointing unmistakably to their specific site of origin, this applies not infrequently to carcinomas of the kidney, thyroid and liver and occasionally to carcinomas of the prostate, uterus and intestine. Further, tumours of similar histological type may exhibit different behaviour according to their

different sites of origin, e.g. epidermoid carcinomas of the skin, lip or larynx are in general slower in growth and later to metastasize than epidermoid carcinomas of the tongue, pharynx or oesophagus

Apart from these features, which are essentially related to histogenesis, regional grouping of tumours has little value. Any organ or system of the body consists of a variety of tissues each of which may be the source of tumours of its own kind. The tumours of a particular kind of tissue are unlike those of other tissues in the organ but closely resemble in structure and behaviour tumours of that kind of tissue in any other organ or region of the body. Thus a carcinoma of the intestine has much in common with carcinomas of the stomach, lung or breast, but has very little in common with a myoma, or a neurofibroma, or a lymphosarcoma of the intestine. It is the *tissue* of origin not the *organ* of origin, of a tumour on which its peculiar properties depend.

(2) Embryological classification

The best known attempt to classify tumours on an embryological basis was that of Adam (1909). He distinguished 'teratomata' derived from 'totipotent' cells, 'teratoblastomata' or mixed tumours derived from 'multipotent' cells, and 'blastomata' derived from 'unipotent' cells. The blastomata he divided into two main groups, "lepidomata" (membrane tumours) and "hylomata" (pulp tumours) corresponding to epithelial and non-epithelial tumours. These were subdivided into 'epilepidomata, hypolepidomata and mesolepidomata' and 'epihylomata, hypohylomata and mesohylomata', according to the germ layers from which the various tissues of the body arise. In each of these subdivisions 'typical' and 'atypical' (corresponding to innocent and malignant) tumours were distinguished. Thus a benign papilloma of the skin would be a 'typical epilepidoma', a carcinoma of the colon would be an 'atypical hypolepidoma', and a sarcoma would be an "atypical mesohyloma".

Although Adam's scheme was widely quoted, it had no real merit. It introduced a series of new names with no advantages over the corresponding old ones, and it laid a wholly unwarrantable emphasis on the germ layer derivation of the tissues from which tumours arise. From skin, oesophageal mucosa and the uterine cervix, which are clothed by squamous stratified epithelia derived from ectoderm, endoderm and mesoderm respectively, there arise epidermoid carcinomas of closely similar structure and behaviour. To designate these as three separate classes of tumours 'epilepidomata, hypolepidomata and mesolepidomata' according to the early germ layer origin of the respective tissues is to create artificial distinctions devoid of pathological value or meaning. Worse still, application of this nomenclature in certain regions leads to the artificial cleavage of a homogeneous group of tumours of a single organ. Thus, squamous celled carcinomas of the anterior two thirds of the tongue, which is ectodermal, would be 'epilepidomata', while identical carcinomas of the posterior third, which is endodermal would be "hypolepidomata", and so also papillary growths of the fundus and of the trigone of the bladder would be distinguished as "hypolepidomata and mesolepidomata" respectively. The female external genitalia contain stratified epithelia derived from all three germ layers so that squamous celled carcinomas of the labia majora would be 'epilepidomata' similar growths

of the labia minora would be hypolepidomata, and similar growths of the vaginal orifice above the level of the hymen would be mesolepidomata. Such distinctions are clearly meaningless. Indeed the germ layers the status of which has of recent years greatly declined even for the embryologist are devoid of significance for the pathologist. Ewing (1940), discussing Adams' classification rightly concludes:

The behaviour of tumor cells is very much more influenced by the characters of the cells of origin than by their embryological derivation. The neoplastic process does not consist in retracing the steps of embryological development. Oncology is not a department of embryology but a separate chapter in the biology of the cell.

In other minor ways embryological concepts have been improperly introduced, sometimes deliberately and sometimes unwittingly, into the nomenclature and classification of tumours. Thus it has become a prevalent habit to replace a familiar ending -oma by -blastoma, the usual intention being to suggest that tumours consist of young proliferating cells of this or that type. Thus the term fibroblastoma is used to embrace all of those tumours fibromas and fibrosarcomas which arise from and represent fibrous connective tissue cells. At first sight there may seem little to cavil at in this usage especially as commonly use the name fibroblast to apply not only to immature connective tissue cells in the embryo but to proliferating connective tissue cells in granulation tissue and other proliferative lesions in adults. So also we speak of osteoblasts, lymphoblasts, myeloblasts and so on in reference to proliferating cells of the adult body so that to such names as osteoblastoma or lymphoblastoma, a strong objection can scarcely be sustained. As regards certain other cell types however the blast ending has a specifically embryological significance. Thus the name spongioblast refers to immature embryonic precursors of neuroglial cells. Hence to describe a tumour composed of incompletely differentiated neuroglial cells as a spongioblastoma is to imply embryonic derivation and properties when only anaplasia is present. Similar objections apply to other names in the Bailey Cushing classification of brain tumours—astroblastoma, ependymoblastoma and pinealoblastoma. So also the term myoblast refers specifically to embryonic muscle formative cells so that the wisdom of using the name myoblastoma for a tumour derived from adult muscle is open to question.

These objections to a too facile use of the ending 'blastoma' are all the more cogent because of the existence of certain truly embryonic tumours derived from and composed of immature tissues which have never attained adulthood namely the embryonic tumours of the kidney, adrenal and sympathetic system, retina, liver etc. These are properly given such names as nephroblastoma, neuroblastoma, sympathicoblastoma, retinoblastoma and hepatoblastoma because they actually do consist of embryonic renal, sympathetic, retinal or hepatic cells as the case may be.

(3) Aetiological classification

Ewing, MacCallum and other pathologists have expressed the belief that advance in our knowledge of the causation of tumours will permit more scientific classification. MacCallum even goes so far as to deny the wisdom of attempting

classification on any other basis than aetiology, and he makes the strangely incorrect statement that we know nothing of this. That better knowledge of causation will afford a basis for classification is a vain hope, because (a) a variety of different carcinogenic agents may evoke identical tumours, and (b) a single carcinogenic agent when applied to different tissues, may evoke a variety of tumours. Thus carcinomas of the skin indistinguishable from one another as regards their structure and behaviour may be produced experimentally by the application of such diverse agents as ultra violet light, X rays, arsenic and a variety of carcinogenic hydrocarbons. On the other hand, a single carcinogenic hydrocarbon suitably applied is capable of evoking such diverse growths as squamous celled carcinoma of the skin, adenocarcinoma of the kidney, the sarcomas of soft tissues, osteogenic sarcoma of bone and cerebral glioma (see chapter 4).

(2) In this respect tumours differ radically from inflammatory diseases. In these, the kind of microbic parasite calls forth its own peculiar tissue reactions, and the variations the resulting disease runs its peculiar course. Hence inflammatory diseases are properly classified on the basis of their causation. For tumours, however, no specific relationships between the nature of the external agents and the tissue reactions evoked, the tumours, are apparent. *The neoplastic change in any given tissue possesses qualities which are largely, if not wholly, independent of the kind of stimulus responsible for it.* Causation then can never afford a basis for the classification of tumours.

COMPOUND NAMES

Much confusion has been caused by the use of ill advised compound names for certain tumours. Compound and hyphenated names have been used in three distinct ways and in employing such a name it is important to recognize clearly in which of these three ways it is being used.

(a) Compound names have been used purely descriptively to enumerate the different components or variants seen in the tumour. Thus, in less enlightened days, a teratoma containing muscle, cartilage and glandular tissues might be called a 'rhabdomyo chondro carcinoma', or a sarcoma of bone of pleomorphic structure might be called an 'osteo myxo chondro sarcoma'. The demerits of such stringing together of names are obvious, they are clumsy, unnecessary, and have all too often carried an implication of multiple histogenesis which was quite erroneous or fanciful. Thus the pleomorphic salivary tumours have been called 'chondro myxo haemangio endothelio sarcomas'!

(b) Compound names such as 'adenocarcinoma' or 'fibrosarcoma' are properly used with an intention quite different from (a), the first part of the name is an adjectival prefix descriptive of the second. An 'adenocarcinoma' is not a mixture of adenoma and carcinoma but a carcinoma in which structural evidence of glandular characters is seen. And a 'fibrosarcoma' is not a mixture of fibroma and sarcoma, but a sarcoma of recognizably fibroblastic derivation and structure.

(c) The third way in which compound names are constructed is to

designate genuinely compound tumours. Thus a mammary fibro adenoma consists of two distinct neoplastic tissues a fibromatous component and an adenomatous component both equally demanding recognition in naming the tumour. So also those very rare tumours in which malignant epithelial and non epithelial tissues coexist are properly called 'carcino sarcomas'. The necessity of having compound names of this kind makes it all the more imperative to avoid the bad habit of inventing those of type (a). I suggest that the names of truly compound tumours should be distinguished from compound names of variety (b) made by the mere addition of prefixes by using a hyphen for the one class but not for the other, as has been done in these paragraphs.

THE CLASSIFICATION ADOPTED

The following grouping based solely on histogenesis and behaviour embraces all the usually recognized classes of tumours without involving any great changes in existing nomenclature, and it indicates the order of presentation in Part II of this work in which its defects and inevitable points of overlapping will be pointed out.

(1) Group I Tumours of epithelial tissues

If benign these are papillomas or adenomas, if malignant carcinomas (Names such as adenocarcinoma 'squamous cell carcinoma carcinoma simplex' etc, do not denote different species but merely variations of structure with respect to kind and degree of differentiation.)

(2) Group II Tumours of non-haemopoietic mesenchymal tissues

Benign tumours of the connective skeletal vascular meningeal and muscular tissues are fibroma, myxoma lipoma chondroma osteoma, benign osteoclastoma, synovioma angioma (haemangioma lymphangioma, glomangioma) meningioma, leiomyoma and rhabdomyoma. Malignant members of the same classes receive the generic name 'sarcoma' often with a prefix corresponding to the benign counterpart.

(3) Group III Tumours of haemopoietic tissues

The peculiar nature of the haemopoietic tissues and their tumours especially their production of freely circulating or mobile cells justifies separation from those of the fixed mesenchymal tissues. These tumours are conveniently grouped thus.

(a) Tumours of lymphoid tissue

(i) Follicular lymphoma

(ii) Lymphosarcoma and lymphatic leukaemia

(iii) Hodgkin's disease

(iv) Reticulosarcoma

(b) Myelomatosis and plasmacytoma

(c) Myelogenous leukaemia and chloroma

(d) Primary polycythaemia

(4) Group IV Tumours of neural tissues

This is a diverse group comprising

(a) Gliomas

- (i) Astrocytic gliomas (astrocytoma and "glioblastoma")
- (ii) Oligodendroglioma
- (iii) Medulloblastoma
- (iv) Ependymal glioma
- (v) Pinealoma

(b) Papillary tumours of choroid plexus**(c) Neurilemmoma****(d) Neuroblastoma and ganglioneuroma****(e) Chromaffinoma and carotid body tumour****(f) Retinal and ciliary tumours**

- (i) Retinoblastoma
- (ii) Diktyoma
- (iii) Epithelial tumours of the ciliary body

' (5) Group V Sundry special classes of tumours**(b) Melanoma****(a) Chordoma****(c) Embryonic tumours of viscera**

- (i) Nephroblastoma
- (ii) Hepatoblastoma
- (iii) Embryonic tumours of other parts

(d) Teratomas**(e) Chorion epithelioma**

REFERENCES

- Adams G (1909) *Principles of Pathology* London
 Bremer J L and Weatherford H L (1944) *Textbook of Histology* p 65 Philadelphia
 Bremer J L and Weatherford H L (1944) *Ibid* p 427
 Ewing J (1940) *Neoplastic Diseases* Philadelphia and London
 Kaufmann E (1929) *Pathology* (S P Reimann's translation) p 876 London
 Maximow A A and Bloom W (1944) *Textbook of Histology* p 26 Philadelphia and London
 MacCallum W G (1942) *Textbook of Pathology* p 1047 Philadelphia and London
 Mallory F B (1923) *Principles of Pathologic Histology* p 274 Philadelphia and London
 Muir R (1941) *Textbook of Pathology* p 204 London

CHAPTER 3

INNOCENCE AND MALIGNANCY

"INNOCENT" AND "MALIGNANT" RELATIVE TERMS

THE PREVIOUS chapter admitted the necessity of a behaviouristic sub division of several of the histogenetic groups of tumours, but stressed that the distinction between innocence and malignancy is not fundamental or clear cut. This chapter is to amplify our conceptions of this distinction the arbitrary nature of which may be made apparent at the outset by the following considerations

(1) Borderline tumours

Many histogenetic species of tumours include some growths which occupy the borderline between innocence and malignancy. Good examples of this are afforded by papillary epithelial growths many of which cannot be classed with precision either as benign papillomas or malignant papillary carcinomas. Thus the papillary growths of the bladder exhibit a complete range of structure and behaviour—from the slowly growing wholly superficial pedunculated villous papilloma of uniform fully organized architecture, to the rapidly growing, infiltrative, sessile, irregularly papillary carcinoma. Of many of the intermediate members of such a series, it is difficult to assess the degree of malignancy and to predict their probable course. Some growths with a past history and microscopical structure which lead us to look upon them as benign, may nevertheless prove their essential malignancy by later recurrence infiltration or metastasis. Similar borderline characters are displayed by some of the papillary growths in the intestine larynx thyroid breast, and in ovarian cysts. These and many other instances of borderline behaviour will be described in detail in later chapters.

(2) "Black sheep" in innocent families

Some species of tumours generally looked upon as benign nevertheless include occasional malignant members. Good examples are the osteoclastomas of bone the slowly growing salivary tumours the echondromas and the leiomyomas. On rare occasions tumours of these kinds though clinically and histologically differing little or not at all from their innocent fellows surprise us by metastasizing and their metastases may present an innocent histological structure. Writers have sometimes described this anomalous and unexpected behaviour by using the self-contradictory phrase 'metastasis of benign tumours' (e.g. Lwing 1940). So also Cohnheim and others long ago described as 'simple colloid goitre with metastases' examples of disseminated growths with a microscopical structure closely resembling normal or goitrous thyroid tissue. It need scarcely be said now that such terms are incorrect and misleading. Metastasis is conclusive evidence of malignancy no matter how slow the growth or how well differentiated the structure of a tumour. (See discussion of 'benign metastasizing goitre' by Bell and Simpson.)

(3) The supervention of malignancy in benign tumours

Related to the foregoing characters is the apparent development of malignancy in previously "innocent" tumours. Thus in a previously benign myoma of the uterus a sarcoma may arise, or a seemingly quiescent thyroid adenoma many years old may finally yield widespread metastases in lungs and bones, or a simple polypoid papilloma of the colon may undergo carcinomatous transformation. While in some cases such as these it is clear that a genuine change from innocent to malignant characters has taken place in the tumour, there are other cases in which this interpretation is open to doubt and it is more probable that the growths possessed low grade or borderline malignancy from the beginning. In discussing this problem as long ago as 1906, Bland Sutton well said, 'It is so difficult to decide between the slow growing spindle cell sarcoma, the fibrifying sarcoma and the gelatinous fibroid (myoma), that it is unwise to argue from our present knowledge that innocent connective tissue tumours may undergo transformation into sarcomata.

The more carefully the histology of tumours is investigated the more obvious does it become that the borderland between innocent and malignant species becomes less easily definable." As later sections of the present work will show, however, indubitable examples of the supervention of malignant change in previously benign tumours do occur, and these, no less than the borderline tumours which Bland Sutton so rightly emphasized, also illustrate the purely relative meaning of the terms 'innocent' and "malignant'.

The over emphasis which has been placed on the distinction between innocence and malignancy has arisen because of the prognostic value of this distinction. The clinician's first demand of the pathologist who examines the tumour he has removed is "Is it innocent or malignant?" This habitual query has engendered the notion that every tumour must be either innocent or malignant. A more enlightened modification of the question and one which pathologists should encourage clinicians to ask is "How innocent or malignant is this tumour?"

INNOCENCE AND MALIGNANCY CONTRASTED

Fortunately the distinction for practical purposes between innocence and malignancy, and often some assessment of the probable degree of malignancy, can be made for the majority of tumours. Recalling always that these terms are relative, the distinction depends on the points indicated in the tabular summary. The features outlined in this table must be briefly amplified.

(1) Structure

Tumours of a given cell type vary greatly in the degree of differentiation attained, in some this is as complete as in the corresponding normal tissue, in others anaplasia or lack of differentiation of different degrees is seen.

Most innocent tumours attain a high degree of structural differentiation so that their tissues closely resemble their normal counterparts. A papilloma of the skin consists of overgrown epidermis which is structurally normal except for exaggerated papillation and cornification, a papilloma of the bladder is clothed by a uniform layer of the non-cornifying stratified epithelium characteristic of the urinary tract, and a papilloma of the large intestine consists of unmistakable colonic mucosa. So also a lipoma consists of structurally typical adipose tissue, a leiomyoma of unmistakable plain muscle fibres, a chondroma of cartilage

Malignant tumours on the other hand frequently show imperfect differentiation of varying degrees. Thus many carcinomas while showing unmistakable epithelial characters, lack those details of cellular differentiation and arrangement which enable us to distinguish one particular kind of normal epithelium from another, so that the histological structure alone may not enable us to distinguish carcinomas of the breast stomach or prostate from one another. Other carcinomas more actively growing and cellular, may even lack all recognizable epithelial characters and may be microscopically indistinguishable from highly anaplastic sarcomas, gliomas or growths of other kinds. In general the degree of malignancy of tumours is roughly proportional to the degree to which they fail to attain histological differentiation, the most anaplastic tumours are the most malignant.

	Innocent tumour	Malignant tumour
1 Structure - - -	Structure often typical of the particular tissue of origin	Structure often atypical i.e. differentiation imperfect
2 Mode of growth -	Growth usually purely expansive and a capsule formed	Growth infiltrative as well as expansive so that strict encapsulation is absent
3 Rate of growth - -	Growth usually slow mitotic figures scanty	Growth may be rapid with many mitotic figures
4 End of growth - -	May come to a standstill or regress	Growth rarely ceases usually progressive to a fatal termination
5 Metastasis - - -	Absent	Frequently present
6 Clinical results - -	Dangerous only because of (a) position or (b) accidental complications or (c) production of excess of hormone	Intrinsically dangerous because of progressive infiltrative growth and metastasis

(*Footnote)

Attempts at precise *histological grading* of malignant tumours as an index to their degrees of malignancy are very arbitrary and unscientific. Broders's method of grading which has been widely adopted consists in dividing malignant growths of any given class into four groups according to whether one, two, three or four quarters of the cells appear incompletely differentiated. In view of the great variety of cellular structure to be seen in different members of most classes of tumours and often in a single tumour, the application of Broders's method seems to me to be largely guesswork. Tumours show great cytological variation and the decision as to which cells shall be labelled 'differentiated' or 'undifferentiated', as the case may be greatly depends on the personal bias and preconceptions of the examiner. It is not surprising to learn that different graders reach different conclusions on the same material. All competent pathologists grade tumours to the extent of forming and expressing opinions as to their probable degrees of malignancy from their general histological structure and broad groupings of tumours according to their degree of anaplasia like those of

* C. W. Nicholson rightly suggested the following as a definition of a pathologist's experience: 'It should be pointed out to those whose knowledge of pathology does not extend beyond applied bacteriology that a box of 100's does not put in a class is not enough to make a pathologist be like a young man an infallible married biologist.'

reenough or Healy, are of value Broders's and other similar grading methods give no greater precision by using numbered labels, attached in accordance with certain arbitrarily chosen and highly variable histological characters

It must be pointed out also that the numerical correlations between grading and prognosis advanced by graders in support of their systems are of no real value. Such correlations are bound to appear with *any* system of grading whatever which does not quite ignore the simple generalization of broad parallelism between the degree of anaplasia and the degree of malignancy of tumours in any given group. For individual prognosis, no scheme of grading can attain greater accuracy than the general principle affords. It is to be hoped that the bad habit of recording such diagnoses as 'squamous cell carcinoma grade 2', 'adenocarcinoma grade 3', will soon cease to be a fashion.

To the important general rule that benign tumours are typical and malignant tumours atypical in structure, there are notable exceptions to which reference has already been made. Tumours of the thyroid afford good examples in both directions. On the one hand, some of the benign adenomas of the thyroid contain imperfectly formed vesicles devoid of colloid, or even diffusely cellular areas, on the other hand some of the adenocarcinomas of the thyroid contain areas of typical colloid filled vesicles indistinguishable from normal thyroid tissue. We have already referred to and rejected the notion that innocent tumours metastasize but the very invention of such phrases as "metastasizing goitre", "metastasizing chondroma", "metastasizing myoma", etc. serves to stress the fact that malignant tumours do not always show an atypical structure. As Nicholson pointed out, a squamous celled carcinoma of the skin may attain such a high degree of differentiation that it might well be spoken of as malignant skin. So also some of the visceral carcinomas differentiate so well, in parts at least, that histological identification of the particular region of origin, such as kidney, prostate or bowel is possible. As Foulds says, "It is evident that an elaborate organization of structure and function is consistent with malignancy."

(2) Mode of growth

Many innocent tumours are strictly localized growing purely by *expansion*, so that if surrounded by other tissues, these are thrust aside and compressed, and the tumour is often distinctly encapsulated. This applies to adenomas, myomas, lipomas, and many other benign tumours. However, not all benign tumours are sharply circumscribed. Osteoclastomas show no capsule nor microscopically sharp delimitation from adjacent bony tissue and marrow, and while many fibromas and meningiomas are well circumscribed some members of these species show limited infiltration of neighbouring tissues. Angiomas also are never encapsulated or sharply delimited their vessels merging into the normal ones with which they communicate and mingling with adjacent normal tissues, but most angiomas are malformations and not true tumours.

Besides growing by expansion malignant tumours also grow by *infiltration* i.e. the tumour cells penetrate into the interstices of the surrounding tissues and grow along tissue spaces, lymphatics or blood-vessels. Even when malignant tumours appear to the naked eye to be sharply circumscribed microscopic examination of the margins often reveals that the tumour cells are infiltrating

the neighbouring tissues. Inconspicuous infiltration may be present for long distances beyond the macroscopically visible edge of the growth. It is this marginal zone of infiltration which makes malignant growths so prone to recur after surgical removal unless a wide excision of the surrounding tissues is carried out.

(3) Rate of growth

Most innocent tumours grow only slowly and show few mitotic figures in the tumour cells. Many malignant tumours, on the other hand, grow rapidly, and mitotic figures are readily found in the cells. Anaplastic tumours contain many mitotic figures, and the mitotic activity of a tumour is probably the most reliable single criterion of its degree of malignancy. If in doubt regarding the malignancy or otherwise of a particular tumour, search for mitotic figures in the tumour cells; if several of these are found easily, then the tumour is almost certainly a malignant one. However, not all malignant tumours grow rapidly; many of the well differentiated adenocarcinomas, scirrhus carcinoma simplex, some of the fibrosarcomas, grow slowly and contain relatively few mitotic figures. On the other hand the slowly growing basal-cell carcinomas of the skin often contain many mitotic figures—a remarkable exception to the parallelism between the numbers of mitoses and the degree of malignancy of neoplasms. The duration of mitosis in various tumours is worthy of study; perhaps in the basal-celled growths mitotic figures are numerous, not because of rapid cell division but because of retardation or arrest of the later phases of mitosis just as happens from the action of colchicine. Mitosis in tumours is described more fully in Chapter 8.

(4) End of growth

While most true neoplasms, benign or malignant, grow continuously and indefinitely, spontaneous cessation of growth and retrogressive changes are seen much more frequently in benign than in malignant tumours. This is not infrequent in adenomas of the thyroid or breast, in uterine myomas and in lipomas, fibromas and meningiomas. Retrogressive changes, namely fibrosis, cystic change and calcification, are most familiar in adenomas of the thyroid and myomas of the uterus. At necropsy, small meningiomas heavily calcified and clearly quiescent, are sometimes found. Benign teratomas, especially the so-called 'dermoid cysts' of the ovary, may be seen in a state of senility and quiescence, either when discovered incidentally at operation or necropsy or when surgically removed because of some accidental complication.

Malignant tumours, on the other hand, very rarely cease growing spontaneously but proliferate and extend continuously to a fatal ending. There do occur, however, very rare cases of spontaneous disappearance of proven malignant growths including mammary carcinoma, papilliferous ovarian growths with peritoneal metastases, malignant melanoma, and other tumours. Useful reviews of this subject are those of Gaylord and Clowes (1906), Rohdenburg (1918), Strauss (1927), Frauchiger (1929), Willis (1934), and Ewing (1940).

Complete permanent spontaneous disappearance of a malignant growth is extremely rare if indeed it ever occurs, but this does not detract from the great interest of partial and temporary retrogressions. The factors responsible for

These phenomena are unknown, but the fact that retrogression has overtaken many cases with widespread metastases shows clearly that these factors are systemic and metabolic rather than local. In this connexion we may recall the acceleration of growth which has often been observed in mammary carcinoma during pregnancy and lactation, and the retardation and even quiescence of the growth after weaning. This phenomenon shows that the growth of a malignant tumour is not entirely independent of the general condition of the organism. Its tissues not only draw their nutrition from the body politic, but are affected adversely or otherwise by its metabolic state. It is then not inconceivable that a tumour which is successfully progressing in its nutritive competition with the healthy tissues, and which unhindered will eventually destroy life, may have the balance turned against it by some sudden metabolic alteration of the organism, and it may not be insignificant that cases of spontaneous retrogression of malignant tumours have often given a history of preceding surgical operation or febrile illness. A tumour is not, as we often tacitly assume, something foreign to the body, possessing unlimited independent growth capacity but rather a part of the individual's own tissues, subject like them to the metabolic state of the body and to the largely unknown laws of senescence and death. This conception though rather nebulous, provides at least a plausible view of the curious fluctuations, delays, recrudescences and retrogressions observed in the life history of some neoplasms.

(5) Metastasis

As has already been remarked, the development of discrete secondary growths in other parts of the body is proof of the malignant nature of a tumour, no matter how slow its growth or how 'innocent' its histological structure. Metastasis depends on the infiltrative invasion of lymphatics, blood vessels or serous and other cavities, and the detachment and transfer of tumour particles. These phenomena will be described in Chapters 9 and 10.

Not all malignant tumours produce metastases. Thus rodent carcinomas are acknowledged malignant tumours in that they are locally invasive and destructive yet they rarely or never metastasize. The same applies to the so called "adamantinomas", these also invade and destroy the bones and neighbouring tissues and always recur unless wide excision is undertaken, but they do not produce metastases. So also most of the gliomata are infiltrating and destructive tumours, and the more rapidly growing of them are highly cellular and speedily fatal, yet, apart from occasional dissemination in the cerebrospinal spaces, these tumours never metastasize. In most classes of tumours which frequently produce metastases there occur members which fail to metastasize even after a long period of active growth and the attainment of a great size.

(6) Clinical results

Benign tumours may prove harmful in any of three ways, (a) by virtue of their position, (b) as a result of secondary complications, or (c) in the case of endocrine tumours by the production of excess of hormones. The following examples are illustrative.

(a) Position

An intracranial tumour, e.g. a meningioma, auditory nerve tumour or pituitary adenoma, no matter how well circumscribed or how slow in growth

it may be, is always clinically serious because of its position. A progressively enlarging tumour in the anterior mediastinum e.g. a retrosternal thyroid adenoma or a cystic teratoma will eventually compress the trachea or the great vessels. A benign myoma of the uterus or a benign ovarian tumour during pregnancy may become incarcerated in the pelvis, leading to serious compression of pelvic viscera or to dystocia.

(b) *Accidental complications*

Haemorrhages take place from benign tumours of mucous membranes, e.g. papillomas of the urinary or alimentary tracts, or from submucous tumours which distend or perforate these membranes, e.g. uterine myomas. The same tumours may suffer surface ulceration and infection and infection is particularly serious if it involves a bulky tumour, e.g. a large uterine myoma or a huge mammary fibro adenoma which has distended and perforated the skin. A pedunculated tumour such as a subserous myoma, or an ovarian cystadenoma or teratoma may suffer strangulation by torsion of its pedicle, and a pedunculated tumour in the intestine is liable to initiate an intussusception.

(c) *Production of excess of a hormone*

This is exemplified by the acromegaly or gigantism resulting from an eosinophil adenoma of the pituitary gland by generalized fibrocystic disease of the skeleton accompanying parathyroid adenoma or by the hypoglycaemic attacks observed with insulin secreting adenomas of the pancreas.

Malignant tumours may produce illness in the same three ways, and indeed the dangers of position and accidental complications are much greater with malignant tumours because of their more rapid growth and their infiltrative and destructive properties. In addition, these properties and the related propensity for metastasis give malignant tumours intrinsically dangerous characters not shared by benign tumours. Because of its progressive growth invasive nature and metastasis a malignant tumour cannot grow for long in the body without reaching and seriously affecting some important organ or suffering some serious complication. The question whether malignant tumours bring about cachexia in any specific chemical way warrants discussion in a separate section.

THE CACHEXIA OF MALIGNANT DISEASE

It has been a prevalent idea that "malignant cachexia" is a peculiar specific result of the growth of a malignant neoplasm in the body, attributable to hypothetical poisons elaborated by the growth or to its parasitic utilization of food substances to the detriment of the normal tissues. I have known students to derive from their clinical teaching the impression that malignant cachexia was an almost necessary accompaniment of malignant disease, and that its absence in a case of obscure nature was of diagnostic value in helping to exclude malignancy. I have heard a reputable clinician say that he could often 'spot' a case of malignancy by the characteristic muddy complexion. Such views must be rejected, because (1) no toxic products of tumour growth capable of causing cachexia have been identified (2) the nutritive requirements of tumours is rarely so great as to be a significant contributing factor in undermining health and (3) the presence or absence of cachexia in cases of malignant disease is clearly referable

to the presence or absence of obvious enough harmful effects of the growths on bodily functions. These points require amplification.

(1) The possible formation of toxic substances by tumours

As will be discussed in Chapter 8, much work has been done on the metabolism of tumour tissue, but no peculiar metabolites have been identified. It is true that some rapidly growing tumours produce large amounts of lactic acid, but this substance is readily converted by the liver into glycogen and there is not the slightest reason to think that it contributes to cancerous cachexia. In any case the majority of tumours of slow or moderate rates of growth do not produce unusual amounts of lactic acid.

In cases of advanced cachexia, chemical alterations of great variety and degree have been observed: alterations of blood sugar, of liver glycogen, of nitrogen metabolism, of mineral balance, of the blood picture, of alkali reserve, and the presence of acetone bodies. But these are all clearly the results or components of cachexia and not its primary causes. Similar changes are seen in advanced debility from other causes, such as starvation, chronic gastro-intestinal disease, or tuberculosis. No chemical changes peculiar to malignancy have been observed in malignant cachexia.

Another possibility to be considered is that, from bulky degenerating tumours, soluble products of degeneration might be absorbed into the circulation and might have toxic effects. This possibility must be admitted, but unless bacterial infection supervenes in degenerating growths, there is no positive evidence that the products of degeneration have serious toxic effects. The soluble products of autolysis of tissues are mainly amino acids, uric acid, creatine, creatinine, glycerin, fatty acids and inorganic salts—in fact, the usual split products of proteins, fats and the other constituents of protoplasm, all of which the body is well accustomed to metabolizing and which could not function as toxic agents. Moreover, many cachexia-producing tumours are neither bulky nor degenerated, so that they cannot be a source of autolytic products in any appreciable quantities.

(2) Nutritional demands of tumours

Do tumours harm the rest of the body by stealing food from it? This view, which has been strongly held by some writers, has only to be studied a moment to be seen to be baseless. A tumour which like a foetus increases its total weight by a pound a month is an exceptionally rapidly growing tumour, yet it cannot be contended that increase of a superfluous tissue even at this rate would place an insupportable burden on the alimentary and metabolic functions of the body. On an adequate diet the nutritional state of a pregnant woman does not suffer as a consequence of the rapid growth of 10 pounds or more of foetal tissue. Most tumours, however, have rates of growth much lower than this. Indeed, with many fatal malignant growths, the total mass of tumour tissue in the body at the time of death amounts to only a few ounces. Clearly the nutritive demands of such growths can be but trifling and an altogether negligible factor in causing the cachexia which they brought about.

It may be suggested that it is not the mere bulk in growth of a tumour that matters, but that tumours may have special nutritive requirements and may

deprive the body of unduly large amounts of such essential factors as vitamins special amino acids or the scantier mineral constituents of our diet. This, however, is pure speculation and as we shall see later study of the chemical composition and metabolism of tumours affords no evidence that they have any peculiar nutritive requirements.

(3) Factors contributing to cachexia

Cancerous cachexia is indeed readily accounted for without postulating unidentified toxins or extravagant nutritive demands. It is the result not of any peculiar properties of malignant neoplasia *per se* but of such obviously debilitating factors as starvation, haemorrhage ulceration bacterial infection destruction of functionally vital tissues pain sleeplessness and anxiety.

Consider for example the extreme cachexia of many cases of cancer of the stomach. In large part this is the cachexia of starvation resulting from poor appetite diminished peptic digestion impaired gastric motility pyloric obstruction or all of these. Haemorrhage ulceration and pain also contribute to the result. In some cases extensive metastases in the liver impair hepatic function and so place an extra burden on nutrition and metabolism, jaundice may be added. In other cases peritoneal dissemination leads to recurrent ascites with corresponding loss of proteins and to impaired bowel motility. Metastases in the upper abdominal lymph glands may extend to obliterate the cisterna chyli and thoracic duct doubtless impeding the absorption of digested fats sometimes even chylous ascites may result. Anaemia may result not only from the general impairment of nutrition but also occasionally in more specific ways sometimes through the destruction of the gastric tissue reducing the haemopoietic factor sometimes by widespread metastatic destruction of red bone marrow.

Similar sequences are apparent when cachexia accompanies carcinoma of the oesophagus or of the intestines or indeed any other kind of malignant disease. Carcinomas of the tongue tonsil or pharynx produce cachexia mainly by ulceration haemorrhage infection pain and diminished food intake through dysphagia carcinoma of the uterus by haemorrhage ulceration urinary obstruction and infection and uraemia carcinoma of the breast by local ulceration and infection or more often by the pain and destruction wrought by metastatic growths in liver bones lungs brain and elsewhere and so on. All observant clinicians and pathologists are well aware that the subjects of malignant disease who have been spared such results as those described above do not exhibit cachexia. This is frequently the case with carcinoma of the breast which even in an advanced state with widespread secondary growths may be accompanied by little or no emaciation or anaemia. On the other hand, how great is the cachexia of advanced pulmonary tuberculosis or of an unrelieved chronic pyloric ulcer.¹

There is indeed no such thing as a specifically malignant cachexia. Cachexia means merely debility malnutrition anaemia emaciation from any causes and malignant tumours are one of the most common and least remediable of these causes.

CONCLUSION

Innocence and malignancy are not two distinct biological properties pertaining to neoplasms but merely convenient terms which have become firmly

entrenched in pathology because of their prognostic value. By experience of each histogenetic class of tumours, we have learnt which particular tumours in that class are likely to remain local in their growth and to be curable by local removal and which ones will spread more or less widely and dangerously. The pathologist knows, however, that in most classes of tumours growths of intermediate behaviour occur, for the prognosis of which the bald terms 'innocent' and malignant must be qualified. Between the cellular characters of tumours and their degrees of malignancy there is a broad parallelism, largely based on the inverse relationship of rate of proliferation and degree of differentiation of tumour cells. To this parallelism however, there are many exceptions.

The notion that malignancy implies something new and peculiar added to neoplasia is false. So also is the notion that there is a specific 'malignant' cachexia.

REFERENCES

- Bell F G (1924) *Brit J Surg* 12 331
 Bland Sutton J (1906) *Tumours Innocent and Malignant*, p 10 London
 Broders A C (1921) *Ann Surg* 73 141
 Broders A C (1926) *Arch Path* 2 376
 Cohnheim J (1876) *Virchows Arch* 68 547
 Cowdry E V (1940) *Arch Path* 30 1245
 Ewing J (1940) *Neoplastic Diseases* p 70 Philadelphia and London
 Ewing J (1940) *Ibid* p 45
 Foulds L (1940) *Amer J Cancer* 39 1
 FRAUCHIGER R (1929) Zur Frage der Spontanheilung von Carcinomen Kritische Zusammenstellung *Z Krebsforsch* 29 516
 GAYLORD H R, and CLOWES, G H A (1906) On spontaneous cure of cancer *Surg Gyn Obst* 2 633
 Greenough (1925) *J Cancer Res* 9 453
 Healy W P (1928) *Report Internat Conf on Cancer* p 86 London
 Nicholson G W (1921) *Guy's Hosp Rep* 71 222
 ROHDENBURG, G L (1918) Fluctuations in the growth energy of malignant tumors in man with especial reference to spontaneous recession *J Cancer Res* 3 193 (An admirable account)
 Simpson W M (1926) *Surg Gyn Obst* 42 489
 Strauss O (1927) *Z Krebsforsch* 24 367
 Willis R A (1934) *The Spread of Tumours in the Human Body* p 114 London

CHAPTER 4

THE EXPERIMENTAL PRODUCTION OF TUMOURS

DURING the last three decades our knowledge of the causation of tumours has advanced rapidly. Studies of two kinds have contributed to this advance (a) statistical studies of occupational social and racial factors in the causation of human neoplasms, and (b) studies in the experimental production of tumours in animals by means of chemical and other agents. These two kinds of researches have stimulated each other. The recognition of occupational and other factors in the genesis of certain kinds of human tumours often preceded and indeed gave birth to the successful production of their experimental counterparts. Now however, much of the knowledge gained experimentally has become so precise and so far in advance of that deducible from studies of human material that the general discussion of causation is best commenced with an outline of the experimental achievements.

In the following account only a small fraction of the now enormous volume of published work can be reviewed. For further details and references the reader should consult the papers of Barry *et al* (1935) Cook *et al* (1936) Kennaway and Kennaway (1937) Cook and Kennaway (1938 and 1940) Badger *et al* (1940 and 1942) Willis (1945), and the monograph by Hueper (1942). Staemmler's and Bauer's reviews of occupational tumours (1937) are also useful.

SECTION I

THE CARCINOGENIC HYDROCARBONS

(1) Skin cancers in man due to tars, oils and allied substances

Long before the isolation of carcinogenic hydrocarbons in a pure state an achievement only of the last two decades it had been recognized that those whose occupations exposed them to soot, tar, pitch, mineral oils or creosote were prone to develop cancers of the skin. It was in 1775 that Percival Pott described chimney sweep's cancer of the scrotum, the first clearly recognized occupational cancer. A century later Volkmann described the first recorded cases of paraffin carcinoma of the skin and increasing numbers of tar and oil cancers were reported thereafter. The most useful of the earlier reviews of the subject is that of Ross (1918) and the Report of the International Conference on Cancer (London 1928). Brockbank's monograph on cotton spinner's cancer (1941) and Hueper's book on occupational tumours (1942) contain much valuable information on the historical and technological as well as the clinical and experimental aspects of the subject.

(2) Experimental tar and oil cancer

Knowledge of occupational tar and oil cancers naturally led to attempts to produce tumours experimentally by using similar means. As long ago as 1889 Hanau painted rats with tar and similar substances but produced only chronic dermatitis. If only he had chanced to use mice instead of rats he might have forestalled the first successful experimental production of cancer by a quarter

of a century In 1894 Cazin also was unlucky in choosing another resistant species, the dog, five months tarring evoked no tumours In 1912 Bayon all but achieved success, he observed epithelial overgrowth, but without invasion after the injection of gas tar into the ear of the rabbit, the soil and the agent were suitable, but the duration of the experiment was insufficient

It was the good fortune of two Japanese workers, Yamagiwa and Ichikawa, to apply a suitable agent to a susceptible animal for a sufficiently long time In 1914 and 1915 they reported the development of papillomas and carcinomas in the skin of rabbits ears following long continued application of tar The First World War, however delayed recognition of this achievement, and it was not until 1918, when they again reported their results, that world wide interest was aroused and modern experimental carcinogenesis was fairly launched The carcinogenic properties of oils were first proved experimentally by Leitch in 1922

Experimental tar and oil cancer has been the subject of an enormous volume of research admirably summarized by Woglom in 1926 and by Seelig and Cooper in 1933 Only the barest outline of the main results can be given here It was soon found by many workers that, of the common laboratory animals, only the rabbit and the mouse were highly susceptible to the development of tar cancer of the skin, rats guinea pigs, dogs and fowls were found to be almost completely resistant, even after prolonged applications That other tissues did not necessarily share this resistance was shown by the development of tar sarcomas following repeated subcutaneous injections in rats and in fowls, results which more recent experiments with pure carcinogenic hydrocarbons have confirmed

When a potent tar or oil is applied twice or thrice weekly to the mouse's or rabbit's skin, papillomas often referred to as "tar warts" and often multiple, develop in from 30 to 100 days or longer and carcinoma in from 50 to 500 days or longer Few carcinomas appear in less than 100 days For the mouse the times of appearance of papillomas are nearly the same as for the rabbit, but malignant change takes place much more readily in the mouse For this reason and others, mice have been used much more than rabbits in experiments on carcinogenesis Carcinomas usually develop from tissue which is already papillomatous, and are of the ordinary cornifying epidermoid type While most animals will have developed tumours by the eighth or ninth month, a few tardy tumours will appear later than this and a small proportion of the animals may fail to produce tumours in spite of prolonged tarring

The duration of tarring is important Most mice painted for four months eventually develop tumours a less proportion of those painted for three or two months do so and the tumours appear on the average later than in animals painted for longer periods while many animals painted for only a month or less fail to develop tumours later The important phenomenon of a long latent period between the cessation of tarring and the appearance of tumours, often many weeks or months in mice was particularly stressed by Leitch

Attempts have been made to shorten the latent period and increase the tumour yield by modifying the painted area by trauma, heat or other agents Deelman (1924) and others found that wounds of a tarred area localized and hastened tumour formation and this 'Deelman phenomenon' has been confirmed using pure carcinogenic hydrocarbons (Pullinger, 1943 and 1945) Cramer (1929) found that injury to an already established benign tar wart is apt to precipitate

malignant change Orr (1934) found that subcutaneous injuries by linen sutures or adrenaline injections hastened the development of tar tumours in the overlying epidermis a result confirmed later (1935) using dibenzanthracene Heat apparently does not increase the susceptibility of skin to tar cancer indeed some workers have noted diminished susceptibility Twort and Twort (1936) found that previous applications of oleic acid increased the carcinogenic potency of tar, while lactic acid lanolin and some other substances diminished it

Many workers have observed that different sites show different degrees of susceptibility to the carcinogenic action of tar and oils (e.g Orr, 1935) The interseapular area of mice is more sensitive to tar than the sacral or abdominal skin while the soles of the feet are the most resistant Animals which are sensitive in one area are usually relatively sensitive in another area (Twort and Twort, 1936)

It remains only to add here that in addition to epidermal papillomas and carcinomas certain other kinds of tumours have been produced by tar Reference has already been made to sarcomas following subcutaneous injections of tar in rats and fowls as well as in rabbits and mice But, even surface applications may occasionally induce sarcomatous change in the dermis (Deelman 1922, Leitch 1922) Melanomas following tar applications have been described in mice by Lipschutz (cited by Woglom) and in dogs after very prolonged tarring by Prassey (1938) The phenomenon of increased incidence of tumours of remote sites following skin tarring will be discussed later

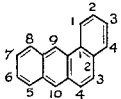
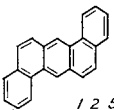
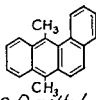
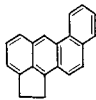
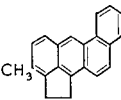

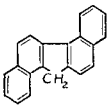
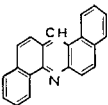
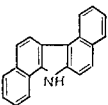

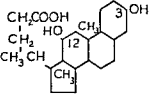

(3) The search for the carcinogenic agents in tars and oils

Since tars and oils are highly complex mixtures of substances and since different tars and oils were found to vary markedly in their carcinogenic efficacy, it soon became evident that a search must be made for specific ingredients responsible for carcinogenesis Many workers (cited by Woglom) investigated the relative efficacy of tars of different kinds of different tar fractions obtained by distillation and of tar extracts made with solvents Notable amongst these was J A Murry (1922) who prepared a highly carcinogenic ethereal extract of tar But by far the most important of the researches into the chemistry of carcinogenic tars were those of Kennaway and his collaborators from 1923 onwards the main results of which were outlined by Kennaway in 1930 These showed that the carcinogenic factor in tar was present in the higher boiling fractions that potent carcinogenic tars could be made artificially by heating acetylene, isoprene skin, yeast, cholesterol or human skin or voluntary muscle to temperatures between 700° and 920° C and that a non-carcinogenic petroleum could be made carcinogenic by heating to 800° C in the process of which aromatic hydrocarbons are formed from those of the aliphatic series Twort and Fulton (1930) prepared highly active tars by heating turpentine and pinene

In 1930 Mayneord and Hieger working with Kennaway made the important observation that the fluorescence spectra of many cancer producing mixtures including gas tar acetylene tar yeast tar muscle tar cholesterol tar ethereal extract of gas tar pitch distillate heated petroleum and shale oil showed the same bands at wave lengths 4 000 4 180 4 400 Å (Hieger) These bands were like those of the fluorescence spectrum of the polycyclic hydrocarbon 1 2 benzanthracene Accordingly Kennaway (1930) made a special study of hydrocarbons

allied to 1 2 benzanthracene, and found 1 2 5 6 dibenzanthracene to be carcinogenic. At last a chemically pure carcinogenic compound had been identified, not indeed as a constituent of tar, but as a result of painstaking studies of the

TABLE I
SOME PURE CARCINOGENIC HYDROCARBONS AND ALLIED SUBSTANCES

 <p><i>1 2 Benzanthracene</i></p>	 <p><i>Dibenzanthracene</i></p>	 <p><i>9 10-Dimethyl-1 2-Benzanthracene</i></p>
 <p><i>Cholanthrene</i></p>	 <p><i>Methylcholanthrene</i></p>	 <p><i>3 4 Benzpyrene</i></p>
 <p><i>1 2 5 6-Dibenzfluorene</i></p>	 <p><i>1 2 5 6-Dibenzacridine</i></p>	 <p><i>1 2 5 6-Dibenzcarbazole</i></p>
 <p><i>3 4-Benzphenanthrene</i></p>	 <p><i>Desoxycholic Acid</i></p>	 <p><i>Beta anthraquinoline</i></p>

physical and chemical characters of carcinogenic tars. Kennaway was careful to point out that "neither benzanthracene nor any of its derivatives have been found and perhaps have not been sought for, in coal tar", and to suggest prophetically

that among the many compounds still undiscovered in tar some might be found far more powerfully carcinogenic than any known substances. So also Hieger in discussing the significance of the discovery of characteristic bands in the spectra of carcinogenic mixtures insisted that the substance responsible for the bands may not be identical with the cancer producer but is some closely allied compound. The carcinogenic agent in tars and oils may be only one of a group of such compounds. The value of the fluorescence test was in Hieger's own words 'to indicate the probability of carcinogenic activity and to assist in directing the preparation of appropriate hydrocarbons'.

(4) Pure carcinogenic hydrocarbons

The importance of the discovery of pure carcinogenic hydrocarbons by the London workers can scarcely be exaggerated. It gave a tremendous impetus to both chemical and biological work in this field. Many new carcinogenic compounds have been produced and tar cancer research has largely been superseded by more precise researches with these chemically pure substances. The number of such substances now runs into scores and only the most important can be mentioned here (See Table I). For more detailed accounts consult the papers of Kennaway and his co-workers already cited, and those of Fieser (1938) and Shear (1938).

(a) Simple derivatives of 1,2-benzanthracene

This substance 1,2-benzanthracene itself is only very feebly carcinogenic but many of its simple substitution derivatives are much more active. This applies particularly to derivatives containing substitution groups at the positions 10, 5, 9 and 6 of the benzanthracene complex. Thus 10-methyl-1,2-benzanthracene, 5-methyl-1,2-benzanthracene, 9-methyl-1,2-benzanthracene and 6-methyl-1,2-benzanthracene have all been prepared synthetically and shown to be active carcinogens in that order of decreasing potency. Further if suitable simple substituents are introduced into two of these favourable positions they then reinforce each other, giving a highly potent carcinogenic compound. This applies to the 5,6, 5,9, 5,10 and 9,10-dimethyl derivatives. The last named is the most active carcinogenic hydrocarbon so far discovered with it Braddury and co-workers obtained skin cancers in mice as early as the 32nd day after the initial application.

(b) Methylcholanthrene and cholanthrene

These merit special interest not only because the former is second only to 9,10-dimethyl-1,2-benzanthracene in carcinogenic activity but also because the cholanthrenes are closely related chemically to the bile acids. Thus methylcholanthrene has been prepared from both desoxycholic acid and cholic acid and both it and the parent hydrocarbon cholanthrene have also been synthesized. Ethylcholanthrene has also been prepared and shown to be an active carcinogen. From the structural formulae (Table I) it will be seen that these compounds again are really 1,2-benzanthracene derivatives with substituents in the carcinogenically favourable positions 10, 5 and 6, methylcholanthrene being particularly notable in that all three of these positions carry substituents.

(c) 3 4 benzpyrene

This is certainly the most active, and perhaps the only important, carcinogenic constituent of coal tar. It was first isolated from coal tar pitch and later prepared synthetically. In accord with Kennaway's 1924 work, the highest boiling fractions of tar contain relatively large amounts of benzpyrene, and the fluorescence spectrum of benzpyrene is of the same type as that of 1 2-benzanthracene. Its close relationship to this substance is evident from its structural formula, which shows that it is really a benzanthracene derivative with an additional benzene ring affecting position 9 where we have already seen substitution is favourable for the development of carcinogenic properties. Benzpyrene is only slightly inferior to methylcholanthrene in potency. Some of its simpler derivatives are also carcinogenic, though less powerfully so than the parent hydrocarbon (Shear, 1939). A high order of carcinogenic activity is shown also by three hexacyclic dibenzpyrenes which have been prepared (Cook and Kennaway, 1938).

(d) 1 2 5 6 dibenzanthracene

This is notable as being the first pure hydrocarbon to be shown to be carcinogenic and since the discovery of this substance, it has been widely used by research workers. It is capable of producing tumours in a high proportion of mice, but it does so relatively slowly. In molecular structure it also is a 1 2 benzanthracene derivative with an added benzene ring as a substituent at positions 5 and 6.

(e) Some other carcinogenic hydrocarbons and related compounds

Certain other hydrocarbons and certain heterocyclic nitrogen containing compounds with structures analogous to the carcinogenic hydrocarbons of benzanthracene type have also been shown to be feebly carcinogenic. These include 1 2 5 6 dibenzfluorene, 1 2 5 6 dibenzacridine, 3 4 5 6 dibenzacridine, 1 2 5 6 dibenzcarbazole and 3 4 5 6 dibenzcarbazole. The ways in which these compounds resemble and differ from the benzanthracene derivatives in molecular structure are shown in Table I. Dibenzcarbazole also produces liver tumours in painted or injected mice (*see later*). It is of interest to find that 3 4 benzphenanthrene and 2 methyl 3 4 benzphenanthrene which are unrelated to benzanthracene, have considerable carcinogenic potency. Morton *et al* (1936) also claimed that triphenylbenzene and tetraphenylmethane were carcinogenic but Cook and Kennaway (1938), Shear (1938) and others have been unable to confirm this. The discovery of Kennaway and co workers, referred to by Badger *et al* that under certain conditions desoxycholic acid, a normal component of bile, can induce sarcomas in mice, is a remarkable one and may prove of far reaching importance.

(5) The relative potency of the carcinogenic hydrocarbons

The relative potency of the various hydrocarbons has been specially studied by Fieser and co authors (1937), Fieser (1938), Iball (1939) and Twort and Twort (1939). Iball after pointing out the difficulties of making accurate comparisons reviewed the results of the London workers as regards the percentage of skin tumours produced and the average period of induction for the various compounds. By dividing the percentage number of tumours by the average induction period in days and multiplying by 100 to give whole numbers, he obtained an index

of potency for each compound. Heading the list was 9,10-dimethyl-1,2-benzanthracene with an index of 151, methylcholanthrene followed with an index of 80, and then benzpyrene with an index of 75. The index for 1,2,5,6-dibenzanthracene was 26 while near the bottom was dibenzacridine with an index of 7. Twort and Twort using a rather different method reached very similar conclusions as regards methylcholanthrene, benzpyrene and dibenzanthracene, the relative potencies of which they found to be roughly in the ratios 10:5:1. The results of the American workers were in general agreement with these.

The solvent used influences the carcinogenic properties of the hydrocarbons when applied to the skin. Benzene has been the most frequent solvent, but Crabtree (1940) found the rate of induction of tumours by benzpyrene to be much faster when ether plus 2 per cent liquid paraffin was used instead of benzene while acetone plus 2 per cent liquid paraffin was found to be much superior to benzene as a solvent for dibenzanthracene. Bradbury and co-workers also found acetone a favourable solvent. Twort and Twort found the relative potencies of dibenzanthracene when dissolved in chloroform, a lowly carcinogenic mineral oil, oleic acid and liquid paraffin to be 60:26:22 and 3.5 respectively. The importance of the solvent doubtless has a bearing on the relative carcinogenic activities of different tars and other crude mixtures. Shear (1938) has pointed out that rabbits, though susceptible to the action of tar, are more refractory to pure carcinogenic hydrocarbons than rats or mice, and that there is experimental evidence of the presence of a reinforcing co-carcinogen in certain tar fractions which are themselves not carcinogenic.

(6) The production of sarcomas by carcinogenic hydrocarbons

In the story of tar cancer reference was made to the development of sarcomas following subcutaneous injection of tar and also following tar painting of the skin. The discovery of highly potent pure carcinogenic compounds greatly facilitated the experimental production of sarcomas. The first contribution in this field was that of Burrows, Hieger and Kennaway (1932) who by subcutaneous injections of 1,2,5,6-dibenzanthracene in lard, obtained transplantable spindle-celled sarcomas in mice and rats. In 1933 Peacock reported similar results in fowls. Further experiments by the London workers were described by Barry and Cook (1934), and in 1935 Boyland and Burrows reported a series of 36 spindle-celled sarcomas obtained in rats and mice by repeated subcutaneous or intraperitoneal injections of colloidal aqueous solutions of dibenzanthracene. Another large series of subcutaneous sarcomas produced by dibenzanthracene was reported by Haagensen and Kruhbiel (1936) who described the histological structure of the tumours in some detail. Of 49 sarcomas they classified 11 as fibrosarcomas, 6 as leiomyosarcomas, 10 as rhabdomyosarcomas (though cross striations were not found and the authors admit that this designation is uncertain) while 22 tumours of poorly differentiated types remained unclassified. Haagensen and Kruhbiel also described a liposarcoma produced by benzpyrene. Mayneord and Parsons (1937) found that X-ray irradiation of mice either previous to or during a series of injections of a soluble derivative of 1,2,5,6-dibenzanthracene accelerated tumour formation and increased the number of sarcomas obtained.

The researches of Shear (1936 and 1938) were of special interest. He obtained sarcomas in mice following the introduction into the subcutaneous tissues of

measured amounts of dibenzanthracene in cholesterol pellets, and found that amounts as small as 0.0004 milligram might be followed by the development of transplantable sarcoma. This is the smallest effective dose of a carcinogen so far recorded, and it serves to show how difficult it might be to isolate and identify naturally occurring carcinogenic substances in tissues. Using pure methylcholanthrene crystals, Shear also found that, prior to the development of tumours, the thickened tissue at the site of injection gave rise to tumours when transplanted to another animal. Transplants about 7 weeks after injection gave rise to tumours as did also a slightly enlarged adjacent lymph gland. These results were not due merely to the transfer of the hydrocarbon in the transplant, because transplants taken at an earlier stage gave negative results. In injected mice not used for transplant experiments, tumours were apparent as early as the 58th day and there were some tumours in all of five different batches of animals by the 75th day. It was clear therefore that methylcholanthrene was a very potent and speedy sarcoma producing agent. Cholanthrene produced sarcomas about as quickly, but crystalline benzpyrene was a little slower. In his 1938 study Shear described the production of subcutaneous sarcomas by various methyl derivatives of 1,2-benzanthracene, the most potent compounds being the 10 methyl, 5,10 dimethyl and 5,9 dimethyl derivatives. Shear also described experimental evidence that mechanical trauma did not promote sarcoma production by methylcholanthrene.

Boyland and Warren performed a series of experiments which showed that different strains of mice varied in their susceptibility to the sarcoma-producing effect of methylcholanthrene.

Orr (1939) made a careful study of the sequence of histological changes leading to sarcoma in the subcutaneous tissues of mice after the introduction of paraffin pellets containing various carcinogenic hydrocarbons. These substances appeared to prevent the occurrence of an adequate fibrous reaction around the pellet, and Orr's results suggest that the development of sarcoma is closely related to this frustrated encapsulation of the foreign body. Peacock and Beck found that sarcoma following injections of benzpyrene developed not in immediate contiguity with the carcinogen, but in the tissues a few millimetres away.

Bonser and Orr (1939) described 160 tumours induced in mice by the subcutaneous administration of carcinogenic hydrocarbons. Sarcomas, which comprised 65 per cent of the tumours in females and 96 per cent in males, were spindle celled and pleomorphic celled growths with much variety of structure, sometimes recalling leiomyosarcoma and sometimes very vascular and possibly angiosarcomatous. Giant celled tumours were common, resembling those designated 'rhabdomyosarcoma' by Haagensen and Krehbiel, but Bonser and Orr saw no evidence that their tumours had arisen from muscle fibres. Of considerable interest was the development in 23 female mice of adenocarcinomas, usually along with sarcoma as well. The origin of these adenocarcinomas was almost certainly from mammary tissue near the site of the injection, a result confirmed in some later experiments. Some squamous celled carcinomas also appeared arising probably from epidermis or from squamous epithelium developed in relation to the injection masses or by metaplasia of other tumours. Some tumours were designated carcino sarcomas because they appeared to consist of two independent components, i.e. spindle celled sarcoma combined with either adenocarcinoma or squamous celled carcinoma.

Not only soft tissue sarcoma, but also sarcoma of bone has been induced by carcinogenic hydrocarbons. Brunschwig and Bissell saw an osteosarcoma of a mouse's tibia 8½ months after an intramedullary injection of benzpyrene.

Following tar applications or the administration of carcinogenic hydrocarbons by various routes several workers have observed the development of leukaemia or leukaemoid states or of lymphomas or lymphosarcomas or, in strains of animals subject to spontaneous lymphoid tumours an increased incidence and earlier development of these growths (Furth and Furth 1938 Brues and Marble 1939 Mider and Morton 1939 Law, 1941).

The production of sarcomas by the same carcinogenic agents which evoke tumours in epithelial tissues is of great interest as regards the nature of neoplasia. It suggests that in spite of the great diversity in the origin, structure and behaviour of tumours the neoplastic change is probably fundamentally similar in all tissues and that gains in our knowledge of the nature of this change in any one tissue will probably shed light on the entire cancer problem.

(7) The production of visceral carcinomas by carcinogenic hydrocarbons

Prior to the discovery of pure carcinogenic hydrocarbons sporadic attempts were made to produce experimental tar tumours of various viscera such as the stomach, gall bladder, bladder, vagina and uterus. Occasional apparent successes were claimed but as these were few and the interpretations often open to doubt we will not discuss them further here (References in Woglom's review). With the discovery of pure carcinogenic compounds however much more extensive and precise studies could be undertaken in this field. We will briefly describe the results achieved in the principal organs concerned.

(a) *The lungs*

In 1925 Murphy and Sturm observed that a high percentage of mice receiving tar applications to the skin developed epithelial tumours of the lungs. In various experiments 60 to 78 per cent of tarred mice developed lung tumours while no tumours were found in control mice even at more advanced ages. The tumours were small white nodules frequently multiple and microscopically identical with the well known adenomas or adenocarcinomas first fully described by Tyzzer. Later workers found that similar results followed the administration of pure carcinogenic hydrocarbons either by surface application or by other routes. Furth and Furth observed increased lung tumours in mice following intrasplenic injections of benzpyrene.

A notable paper is that of Magnus (1939) who attempted to produce gastric cancer in mice by introducing 1,2,5,6-dibenzanthracene twice weekly directly into the stomach. No gastric tumours developed but tumours of the lungs appeared in 95 per cent of the animals as against 4 to 8 per cent of controls. The induced lung tumours resembled those occurring spontaneously but three-quarters of them showed histological signs of malignancy with metastasis in two mice.

Shumkin (1939) reviewed those experiments which have shown an increased incidence of lung tumours following administration of carcinogens by various routes. In Shumkin's own experiments the routes were intratracheal and intravenous. In a strain of mice with a natural incidence of lung tumours of about

20 per cent a single administration of 0.1 milligram of methylcholanthrene or of dibenzanthracene dispersed in a horse serum and cholesterol vehicle, produced multiple lung tumours in almost all treated animals surviving four months or longer. After intravenous injections, nearly all mice given methylcholanthrene and about 60 per cent of those given dibenzanthracene, developed lung tumours. In view of the efficacy of injected material in producing lung tumours in mice, it appears probable that the substances however applied, reach the susceptible lung tissue via the circulation after absorption in small amounts from the site of application. Experiments by Lettinga (cited by Cook and Kennaway) confirm this view. Mice were given graded amounts of dibenzanthracene subcutaneously, those receiving small amounts developed few lung tumours, often no more than control animals, while those given large amounts frequently developed many tumours, up to 40 or more in one animal. This result strongly suggests overflow and systemic absorption of the carcinogenic agent from the site of injection. Evidently then a locally acting carcinogenic agent may also act on a susceptible tissue remote from the site of initial application of the agent, a phenomenon which may possibly be of great significance as regards some kinds of spontaneously occurring neoplasms. (Experimental work on inhaled dusts and lung tumours is discussed later.)

(b) *The kidney*

Ilfield (1936) inserted cholesterol pellets containing carcinogenic hydrocarbons into various viscera of mice and rats, and obtained his most successful results in the kidneys. All of 12 renal tumours induced in this way were of epidermoid type, suggesting an origin from the renal pelvis. Adenocarcinomas of the renal parenchyma in rats which had been given subcutaneous injections of β anthraquinoline, the structural formula of which closely resembles that of 1,2-benzanthracene were observed by Semproni and Morelli (1939). Should this result be confirmed, it will illustrate a remote selective effect of the agent on renal tissue.

(c) *The alimentary canal*

Many experiments (cited by Magnus, Peacock and Kirby, and Cook and Kennaway (1940)) in which carcinogenic hydrocarbons have been administered by ingestion, have failed to produce tumours of the stomach or intestines or the apparently successful results have been unconvincing or too few to be certainly significant. Negative results are not surprising in view of the brief duration of contact of the material with any given area of mucosa its dilution with food, and the probable protective action of mucus. However Waterman, Peacock and Kirby Badger *et al.*, and others have reported tumours of the stomach in mice after feeding with benzpyrene methylcholanthrene or other substances, and it is not unlikely that further experiments will reveal the conditions necessary in order to produce alimentary carcinomas by ingestion of carcinogenic substances. It must be added that great caution is necessary in assessing the significance of apparently successful production of gastric tumours in rodents since vitamin deficiency can cause tumour like proliferations (Passey Beck and Peacock, Brunschwig and Rasmussen), and since some strains of animals spontaneously develop many adenomatoid lesions (Stewart and Andervont).

(d) *The liver*

Ilfield obtained carcinoma of the mouse's liver by locally introduced dibenzanthracene pellets. It is also of interest that 3,4,5,6-dibenzcarbazole, applied to the skin of mice, may produce bile duct proliferation and hepatoma like tumours (Cook *et al.* 1936) not only because this again shows action at a distance but also because this substance is related chemically to β -naphthylamine to be discussed later.

(e) *The genital system*

Following repeated intratesticular injections of dibenzanthracene in rabbits Lacassagne saw an adenocarcinoma probably of the epididymis in one animal. Also by locally introduced carcinogenic agents Ilfield obtained uterine carcinoma in mice and Moore and Melchionna carcinomas and sarcomas of the prostate in rats. Burrows and Boyland suggested that just as the incidence of spontaneous lung tumours in mice is increased by a carcinogenic compound given by almost any route so it is possible that the incidence of uterine adenoma and carcinoma in rabbits may be increased by either local or remote applications of carcinogenic hydrocarbons. But they were careful to point out that since uterine tumours often occur spontaneously in the rabbit their experiments did not prove conclusively that their dibenzanthracene applications had indeed played a part.

(f) *The breast*

We have already noted Bonser's experiments (1939 and 1940) in which mammary adenocarcinomas were evoked by neighbouring subcutaneous injections of carcinogens. Orr (1943) obtained many mammary carcinomas in mice of breeds which did not naturally develop such tumours by means of intranasal administration of methylcholanthrene.

(g) *The salivary glands*

Franseen and co-workers obtained epidermoid carcinomas of the salivary glands in rats and mice following the local introduction of carcinogens.

(8) *The production of tumours of the nervous system by carcinogenic hydrocarbons*

Seligman *et al.* (1939) described 11 gliomas and 2 fibrosarcomas which developed in the brains of mice following the intracerebral implantation of methylcholanthrene pellets. In structure the gliomas closely resembled the various types seen in human beings. One of the tumours was successfully transplanted. Confirmatory results were obtained by Piers and by Zimmerman and Arnold. In some similar experiments of my own in 1934 and 1936 the introduction of pure crystalline dibenzanthracene into the brains of 30 rats failed to produce any tumours in periods ranging from 6 to 12 months. Possibly these times were insufficient for the relatively slowly acting carcinogen or possibly the rat is less susceptible than the mouse to the induction of gliomas.

(9) *Remote action of carcinogens*

Experimental work shows unmistakably that carcinogenic hydrocarbons may be absorbed from their initial site of application and may then be effective in evoking tumours in other susceptible tissues. We have already noted the increased

incidence of lung tumours and of lymphoid tumours in susceptible mice, following administration of carcinogens by almost any route, and a similar increased incidence of liver tumours has been observed. In Orr's experiments already cited in which mammary carcinomas resulted from the intranasal administration of methylcholanthrene, it seems clear that the carcinogen could not have contaminated the breasts in any direct way but must have reached them after absorption. Bridger *et al* record instances of multiple tumours of several different tissues following injections or ingestion of potent hydrocarbons. Of interest in this connexion are the studies of Percock and others on the absorption, distribution and fate of polycyclic hydrocarbons in the body.

(10) Constitutional factors influencing carcinogenesis by hydrocarbons

When a carcinogenic agent is applied to a number of mice of mixed stock, there is much individual variation in the date of development of tumours and some animals may never develop tumours even after long periods. Further different inbred pure strains of mice differ in their susceptibility to carcinogenic agents. It is possible by selective breeding to produce a race of mice specially sensitive to the action of tar and pure carcinogenic hydrocarbons on the skin (Bonser 1938). Such animals do not necessarily show increased susceptibility of other tissues: indeed Bonser later (1940) found that her skin susceptible mice were less susceptible than other strains to the induction of sarcoma by subcutaneous injections of methylcholanthrene.

Since the incidence of mammary tumours in inbred strains of mice is known to depend partly on genetic factors, various workers have attempted to trace a relationship between the incidence of breast tumours and the susceptibility to carcinogenic agents applied to the skin or injected. Thus Crimer (1936) and others concluded that the skin of animals prone to develop mammary cancer was definitely resistant to the action of carcinogens, and postulated an hereditary antagonism for carcinogenesis in the two sites skin and mamma. The results of other workers (cited by Bonser) have not confirmed this view, there is great variation in the results obtained in different laboratories. It appears probable that each kind of tissue in each strain of mice has its own type of carcinogenic response, and that the susceptibilities of different tissues, such as skin and breast, are independent of one another.

(11) The mode of action of carcinogenic hydrocarbons

The way in which hydrocarbons induce neoplastic change is still obscure. Relevant to the problem are (a) the pre-cancerous histological changes in tissues exposed to these agents (b) the state of the tissues during the latent period which may intervene between exposure to the agent and the appearance of tumours (c) co-carcinogens and anti-carcinogens (d) the effect of carcinogenic hydrocarbons on tissue cultures (e) and on lower animals or plants and (f) the chemical changes taking place in carcinogens in the tissues.

(a) *Histological changes in tissues exposed to carcinogenic hydrocarbons*

Early observations on the pre-cancerous changes in tarred skin well described by Deelman (1923) and by Woglom were difficult to interpret because non-specific irritative changes due to the crude mixtures were present. The preparation

of chemically pure hydrocarbons obviated this and permitted study of the early pre-cancerous changes evoked by the carcinogen alone. However the work of Deelman and others on the histogenesis of tar tumours provided much essential information which the later studies with pure carcinogens confirmed and amplified. The changes observed in tarred mouse skin were hyperplastic thickening and stratification of the epidermis accompanied by increased mitosis in the basal layer leading on to the development of papillary outgrowths and later atypical growth with irregular cornification accompanied by increased mitosis in all layers going on to invasive carcinoma. Deelman's work showed clearly that these proliferative changes affected a considerable area of epidermis and that the development of papilloma and carcinoma in this area was demonstrably multicentric and multicellular.

Using methylcholanthrene and cholanthrene Page (1938) found that mouse epidermis showed a prompt increase in the size of the nuclei and nucleoli which he believed to be due to a direct stimulating effect of the carcinogen on these structures. Cowdry and Palitta (1941) in a careful study of the pre-cancerous hyperplasia induced in epidermis by methylcholanthrene observed a progressive increase in nuclear and cytoplasmic volumes of both basal and spinous cells with increased mitosis especially in the basal cells. Increase of nucleolar size took place in the later stages of hyperplasia. Cowdry and Palitta felt unable to state whether the increased mitosis in the hyperplastic epidermis was a direct or indirect effect of the carcinogen. These workers had found also that intranuclear viscosity measured by the displacement of nuclear contents by centrifugation was slightly diminished during pre-cancerous hyperplasia and greatly diminished in actively carcinomatous cells and that similar changes occurred also in human tissues. They suggested therefore that changes of cytoplasmic and nuclear volumes during carcinogenesis may be related to changes of mineral and water content. Pullinger (1940 and 1941) found that the hyperplasia induced in epidermis by a single application of a carcinogenic hydrocarbon appeared to be specific and unlike that following the application of non-carcinogenic substances. Law (1941) using a race of mice highly sensitive to carcinogens applied to the skin obtained multiple papillomas and carcinomas following single applications of 9-10-dimethyl-1,2-benzanthracene.

Glucksmann (1945) has reviewed previous work on the structural changes in mouse skin following applications of carcinogenic hydrocarbons and has carried out further studies on the response to benzo(a)pyrene. The primary response comprised increased mitosis with increase in both number and size of the cells and delay of differentiation and these changes affected the whole of the treated area. Papillomas and carcinomas appeared as foci of increased overgrowth and disturbed differentiation and lateral expansion of papillomas is a result of increased growth of adjacent hyperplastic regions and not of lateral migration of papilloma cells and their multiplication. Malignant change appeared to be a gradual process since it is impossible to find a clear demarcation line between malignant cells and their non-malignant neighbours. Even fairly small foci are not sharply outlined.

Orr's work (1938) while not denying the importance of the proliferative changes in the epithelium reminds us not to overlook the possible influence of

incidence of lung tumours and of lymphoid tumours in susceptible mice, following administration of carcinogens by almost any route, and a similar increased incidence of liver tumours has been observed. In Orr's experiments already cited, in which mammary carcinomas resulted from the intranasal administration of methylcholanthrene, it seems clear that the carcinogen could not have contaminated the breasts in any direct way but must have reached them after absorption. Badger *et al* record instances of multiple tumours of several different tissues following injections or ingestion of potent hydrocarbons. Of interest in this connexion are the studies of Peacock and others on the absorption, distribution and fate of polycyclic hydrocarbons in the body.

(10) Constitutional factors influencing carcinogenesis by hydrocarbons

When a carcinogenic agent is applied to a number of mice of mixed stock there is much individual variation in the date of development of tumours and some animals may never develop tumours even after long periods. Further, different inbred pure strains of mice differ in their susceptibility to carcinogenic agents. It is possible by selective breeding to produce a race of mice specially sensitive to the action of tar and pure carcinogenic hydrocarbons on the skin (Bonser, 1938). Such animals do not necessarily show increased susceptibility of other tissues, indeed, Bonser later (1940) found that her skin susceptible mice were less susceptible than other strains to the induction of sarcoma by subcutaneous injections of methylcholanthrene.

Since the incidence of mammary tumours in inbred strains of mice is known to depend partly on genetic factors, various workers have attempted to trace a relationship between the incidence of breast tumours and the susceptibility to carcinogenic agents applied to the skin or injected. Thus Cramer (1936) and others concluded that the skin of animals prone to develop mammary cancer was definitely resistant to the action of carcinogens and postulated an hereditary antagonism for carcinogenesis in the two sites, skin and mamma. The results of other workers (cited by Bonser) have not confirmed this view, there is great variation in the results obtained in different laboratories. It appears probable that each kind of tissue in each strain of mice has its own type of carcinogenic response and that the susceptibilities of different tissues, such as skin and breast are independent of one another.

(11) The mode of action of carcinogenic hydrocarbons

The way in which hydrocarbons induce neoplastic change is still obscure. Relevant to the problem are (a) the pre cancerous histological changes in tissues exposed to these agents (b) the state of the tissues during the latent period which may intervene between exposure to the agent and the appearance of tumours (c) co carcinogens and anti carcinogens (d) the effect of carcinogenic hydrocarbons on tissue cultures (e) and on lower animals or plants and (f) the chemical changes taking place in carcinogens in the tissues.

(a) Histological changes in tissues exposed to carcinogenic hydrocarbons

Early observations on the pre cancerous changes in tarred skin well described by Deelman (1923) and by Woglom were difficult to interpret because non-specific irritative changes due to the crude mixtures were present. The preparation

of chemically pure hydrocarbons obviated this and permitted study of the early pre-cancerous changes evoked by the carcinogen alone. However the work of Deelman and others on the histogenesis of tar tumours provided much essential information which the later studies with pure carcinogens confirmed and amplified. The changes observed in tarred mouse skin were hyperplastic thickening and stratification of the epidermis accompanied by increased mitosis in the basal layer, leading on to the development of papillary outgrowths, and later, atypical growth with irregular cornification accompanied by increased mitosis in all layers going on to invasive carcinoma. Deelman's work showed clearly that these proliferative changes affected a considerable area of epidermis and that the development of papilloma and carcinoma in this area was demonstrably multicentric and multicellular.

Using methylcholanthrene and cholanthrene Page (1938) found that mouse epidermis showed a prompt increase in the size of the nuclei and nucleoli which he believed to be due to a direct stimulating effect of the carcinogen on these structures. Cowdry and Paletta (1941) in a careful study of the pre-cancerous hyperplasia induced in epidermis by methylcholanthrene observed a progressive increase in nuclear and cytoplasmic volumes of both basal and spinous cells with increased mitosis especially in the basal cells. Increase of nucleolar size took place in the later stages of hyperplasia. Cowdry and Paletta felt unable to state whether the increased mitosis in the hyperplastic epidermis was a direct or indirect effect of the carcinogen. These workers had found also that intranuclear viscosity measured by the displacement of nuclear contents by centrifugation was slightly diminished during pre-cancerous hyperplasia and greatly diminished in actively carcinomatous cells and that similar changes occurred also in human tissues. They suggested therefore that changes of cytoplasmic and nuclear volumes during carcinogenesis may be related to changes of mineral and water content. Pullinger (1940 and 1941) found that the hyperplasia induced in epidermis by a single application of a carcinogenic hydrocarbon appeared to be specific and unlike that following the application of non-carcinogenic substances. Law (1941) using a race of mice highly sensitive to carcinogens applied to the skin obtained multiple papillomas and carcinomas following single applications of 9,10-dimethyl-1,2-benzanthracene.

Glucksmann (1945) has reviewed previous work on the structural changes in mouse skin following applications of carcinogenic hydrocarbons and has carried out further studies on the response to benzo(a)pyrene. The primary response comprised increased mitosis with increase in both number and size of the cells and delay of differentiation and these changes affected the whole of the treated area. Papillomas and carcinomas appeared as foci of increased overgrowth and disturbed differentiation and lateral expansion of papillomas is a result of increased growth of adjacent hyperplastic regions and not of lateral migration of papilloma cells and their multiplication. Malignant change appeared to be a gradual process, since it is impossible to find a clear demarcation line between malignant cells and their non-malignant neighbours. Even fairly small foci are not sharply outlined.

Orr's work (1938) while not denying the importance of the proliferative changes in the epithelium reminds us not to overlook the possible influence of

vascular and other changes in the subepithelial connective tissues. In his experiments invasive carcinoma appeared to develop most usually in relation to areas of damaged elastic tissue and dermal scars.

As to the mode of development of sarcomas following the subcutaneous introduction of carcinogens, Orr (1939) found that, while implanted pellets of paraffin or of paraffin containing non carcinogenic hydrocarbons incited the usual foreign body reaction and were finally encapsulated in fibrous tissue, this was not the case with pellets containing potent carcinogenic substances. The newly developed tissue around such pellets was deficient in quantity and quality and no effective fibrous encapsulation eventuated. The development of sarcoma, which took place in the tissues marginal to and often at some distance from the pellets, thus appeared to be related to a deficient or frustrated foreign body response occasioned by the presence of the carcinogen. Other workers also (e.g. Peacock and Beck) have observed that sarcomas may arise from the tissues some distance marginal to the introduced material.

(b) *Latent pre cancerous changes*

It has been shown repeatedly that, following applications of a carcinogenic hydrocarbon for a limited period, the tissues may then show little or no structural change during a quiescent phase of short or long duration, and yet tumours may subsequently appear. This latent period was subjected to close experimental study by Rous and Kidd and by MacKenzie and Rous (1941). These workers showed that, when tar is applied for a period insufficient to induce tumours in rabbits, the epithelium, though thereafter apparently normal and quiescent, has nevertheless received a bias towards future tumour formation. For if tarring is recommenced later for a short period, papillomas may speedily appear. Cessation of tarring may now be followed by regression of the papillomas, and a subsequent course of tarring may promptly re-evolve them. In this way a particular papilloma may be made to disappear and reappear repeatedly, but each time it reappears more promptly and regresses more slowly. Finally, no retrogression occurs even when tarring is permanently discontinued, and the papilloma grows progressively and becomes malignant. According to the view of Rous and his colleagues, continuous tarring induces a continuous succession of imperceptible stages, while intermittent applications induce changes up to a certain point with each application. In the intervening tar-free periods, the cells already prepared to become cancerous on slight additional provocation may nevertheless lie quiescent for long periods until the additional provocation of resumed tarring or of some non-specific irritant or a trauma, precipitates them into progressive uncoordinated growth. These experimental findings recall and amplify those of Deelman, Pullinger and others already referred to, which show that injury of a carcinogenically prepared area may precipitate tumour formation. Lavik and co-workers (1942) have confirmed the cumulative effects of successive applications of carcinogens: the initial applications produce subcancerogenic changes in the tissues, so that repainting after a long interval may rapidly induce tumours.

(c) *Co carcinogens and anti carcinogens*

The preceding account shows that the application of a carcinogenic hydrocarbon to a susceptible tissue leaves an indelible effect on the tissue such that

subsequent applications of stimuli not in themselves carcinogenic may yet evoke neoplasia. Such stimuli, which may be called co-carcinogenic might also operate during the application of the carcinogen itself. Thus, Shear and others have advanced reasons for believing that tars and tar fractions contain substances which reinforce the action of the carcinogenic constituents and Berenblum (1941) showed that croton oil applied with or after benzpyrene augmented the potency of this substance. On the other hand carcinogenesis by hydrocarbons is inhibited by mustard gas (Berenblum 1935) and by bromobenzene and certain other halogen compounds (Crabtree 1943).

(d) *Effect of carcinogenic hydrocarbons on tissue cultures*

No worker has yet proved the induction of neoplastic change in tissue cultures treated by carcinogens. The few experiments which have been done were reviewed by Cook and Kennaway (1940) and by Earle and Voegtlin (1938) whose own work showed retardation of growth and degenerative changes in cultures of rat and mouse fibroblasts treated with methylcholanthrene even in low concentrations. Morton stated that Gey had observed neoplastic change in cultures of rat fibroblasts and that a report was in the press but as far as I know this has not appeared. More experiments in this field are needed. Lewis and Doljanski and Halbertsma found that pure cultures of a benzpyrene induced rat sarcoma retained their malignant properties *in vitro* and regularly produced tumours on reimplantation into rats.

(e) *The effect of carcinogenic hydrocarbons on lower animals and plants*

This has been the subject of a few scattered observations which briefly summarized by Page, by Earle and Voegtlin and by Cook and Kennaway (1940) have included yeast, plant roots, hydroids and planarians in all of which some stimulation of growth has been reported. Of special interest are Mottram's experiments (1941) with paramecia and other ciliates treated with carcinogenic hydrocarbons and other agents. These protozoa showed signs of increased cytoplasmic viscosity and various nuclear and mitotic abnormalities and the abnormal organisms transmitted similar abnormalities to their descendants. Mottram looked upon these abnormalities as analogous to the cellular pleomorphism and anaplasia of malignant tumours and suggested that protozoal studies may afford the simplest way of analysing the essential characters of the neoplastic change. This change may be primarily cytoplasmic rather than nuclear for the cytoplasm contains important components such as mitochondria and Golgi apparatus which may be the main points of action of the carcinogenic agent. Mottram's views are still in the realm of hypothesis but they justify further research along the lines he suggested.

(f) *The chemical changes and fate of carcinogenic hydrocarbons in the tissues*

These were discussed at length in Fieser's paper in 1938. He concluded that it seems clear that the hydrocarbon suffers rapid alteration in the animal body. Some chemical reaction occurs and this apparently exhausts most of the carcinogen long before tumours begin to appear. The most obvious hypothesis is that the reaction in which the carcinogen disappears represents the first step in a time-consuming and complicated chain of events leading eventually to malignant growth. Fieser also referred to certain similarities in the chemical properties

bile duct cystadenoma, but all combinations of these occurred, and multiple tumours were often seen. Miller and Baumann (1945) and Sugiura *et al* (1945) have shown the carcinogenic activity of several new derivatives of dimethyl aminoazobenzene.

(3) Hepatic tumours produced by other agents

Although the azo compounds are highly active and selective as carcinogens for hepatic tissue it is important to recall that they are not the only ones. Reference has already been made to tumours produced by locally introduced hydrocarbons and by cutaneous applications of 3,4,5,6-dibenzcarbazole. Important also is the observation of Edwards (1941) that benign hepatomas can be induced in mice by carbon tetrachloride.

An interesting relationship between the carcinogenic substances of the azo class and the polycyclic hydrocarbons is shown by some work of Cook *et al*. They found that 2,2-azonaphthalene could produce liver tumours in mice, and that the allied substance diamino dinaphthyl was still more potent. This substance readily undergoes deamination to 3,4,5,6-dibenzcarbazole, which, as already mentioned when discussing hydrocarbons, also produces liver tumours as well as skin tumours and sarcomas at the local sites of application.

SECTION III

SUNDRY OTHER CHEMICAL CARCINOGENS

(1) 2-Naphthylamine and bladder tumours


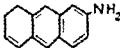
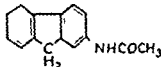
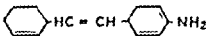
The occupational incidence of papilloma and carcinoma of the bladder in employees in the aniline dye industry was recognized many years before its experimental confirmation by Hueper and co-workers in 1938. Many previous workers (cited by Berenblum and Bonser) had attempted, unsuccessfully, to produce bladder tumours by means of aniline derivatives and allied substances. Hueper and co-workers showed that vesical tumours could be induced in dogs by prolonged administration of 2 (Beta) naphthylamine, a compound related to aniline and frequently present in aniline products. The specific carcinogenic activity of this substance for the epithelium of the urinary tract was confirmed by Bonser (1943). Hueper's book contains an excellent review of the whole subject of the occupational tumours of aniline workers, and of their experimental counterparts. While 2-naphthylamine is the main substance so far incriminated, it is very probable that other aromatic amines or their derivatives will also prove to be occupational carcinogens, and it must not be forgotten that, as mentioned above, azo compounds which are unrelated to aniline, can also evoke urinary tract tumours.

(2) Other aromatic amines

The discovery of Wilson *et al* that continued oral administration of 2-acetylaminofluorene to rats produced epithelial tumours of several different organs, notably the bladder, renal pelvis, liver, pancreas and lung, was confirmed by Bielschowsky (1944) and by Armstrong and Bonser. It appears probable, however,

that different breeds of the same species differ in the localization of the tumours produced. Bielschowsky's Wistar rats showed a high incidence of carcinomas of the liver, breast, external auditory meatus and intestines, and also leukaemias, while in Armstrong and Bonser's mice carcinomas of the bladder were the most frequent tumours as in Wilson and co-workers' rats. Bielschowsky (1945) also obtained adenomas and carcinomas of the thyroid in rats given acetylaminofluorene, and he and Green saw multiple renal carcinomas in a fowl.

TABLE III
STRUCTURAL FORMULAE OF CARCINOGENIC AROMATIC AMINES

 <p><i>2-Naphthylamine</i></p>	 <p><i>2-Anthramine</i> (Aminoanthracene)</p>
 <p><i>2-Acetylaminofluorene</i></p>	 <p><i>4-Aminostilbene</i></p>

Another aromatic amine recently found to be carcinogenic is 2 anthramine (2 aminanthracene). By local applications of this substance to rats Bielschowsky (1946) obtained carcinomas, papillomas and spindle-celled tumours of the painted skin, and occasional remote tumours also including carcinomas of the external auditory meatus.

Work in progress by Haddow, Kon and Harris has shown that 4 aminostilbene and several derivatives are carcinogenic for rats.

(3) A sarcoma producing quinoline-styryl compound

While studying the efficacy of trypanoxidal substances in mice Browning and co-workers (1933 and 1936) discovered that a complex quinoline-styryl compound was highly potent in producing sarcomas at the site of the injection.

(4) Adrenal medullary tumours produced by nicotine

In rats receiving small daily doses of nicotine by subcutaneous injection Staemmler (1945) observed nodular growths of the chromaffin tissue of the adrenal glands. Further work on this interesting result is needed.

(5) Inorganic substances and non-specific irritants

It is probable that previous to the discovery of the specifically carcinogenic substances and when chemical irritation was accepted as an important cause of neoplasia in many experiments were conducted with the ordinary irritants.

and metallic salts in an endeavour to induce tumours. The occasional positive results reported, as by Narat, are of doubtful significance. Burrows (1936) reported that in none of 362 animals did a tumour grow at the focus of chronic irritation caused by injections of silica, bouillon or starch, but that 53 per cent of these animals which lived 4 months or longer developed tumours at other foci into which dibenzanthracene had been injected.

The recognition of chronic arsenical dermatitis, due to occupational exposure or medicinal administration, as an occasional precursor of carcinoma of the skin led to many attempts to produce arsenical cancers experimentally. The first tumour following the experimental use of arsenic was that of Leitch and Kennaway in 1922, and the most recent that of Hueper in 1942. These occasional positive results, however, are still inconclusive, and further work is needed.

The experimental production of teratomas of the testes of roosters by means of intratesticular injections of zinc salts, reported by a group of Russian workers, and confirmed by Bagg in America, is of doubtful significance for mammalian pathology. It is discussed in Chapter 61.

(6) A review of substances tested for carcinogenic powers

With the constant increase in the number and variety of synthetic organic and other compounds handled and eaten by civilized man, thought must be given to the possible carcinogenic properties of many of these. Already, within the last two decades as we have seen several distinct classes of potent carcinogenic compounds have been identified. It is certain that future research will reveal similar potency in other classes of compounds as yet not suspected of it.

The U.S. National Cancer Institute has recently issued a valuable tabular survey of compounds which have been tested for carcinogenic activity, compiled by J. L. Hartwell. This survey covers 696 substances which have been tested, 169 of which have been carcinogenic. These of course include the carcinogenic hydrocarbons and other compounds described above, many of which were tested in the course of deliberate search for likely carcinogenic agents. The future will witness a great expansion of such biological testing of synthetic substances old and new and of the by-products of industrial and technological processes. Hueper's book outlines our knowledge to date and his opening section on the new artificial environment is an arresting reminder of the complexity of the chemical hazards of modern life.

SECTION IV

THE EXPERIMENTAL PRODUCTION OF MAMMARY TUMOURS

(1) Early work on the relationship of ovarian function and mammary tumours

Struck by the fact that tumours of the breast were very common in women and very rare in men and perhaps by the acceleration of growth of mammary cancers during pregnancy and lactation, clinicians long ago suspected some relationship between ovarian activity and breast tumours, and oophorectomy was advocated and practised as a therapeutic measure in cases of mammary cancer. Experimental researches on spontaneously occurring mammary tumours in animals, and the identification of the ovarian hormones, soon led to much more precise knowledge in this field.

Lathrop and Loeb in 1916 found that removal of the ovaries of female mice before the age of six months markedly decreased the subsequent incidence of mammary cancers and that the tumours which did develop in spayed animals appeared at a later age than in normal controls. These effects were not observed in animals spayed at ages exceeding six months. Prevention of breeding also diminished the mammary cancer incidence and increased the age of development of the tumours but less markedly so than spaying. Lathrop and Loeb interpreted their results as due to a chemical influence of the corpus luteum on the mamma, an influence which was superimposed on an hereditary factor of tumour susceptibility. Confirmation of Lathrop and Loeb's experimental results came with the work of Cori (1927), who showed that removal of the ovaries in very young mice of a cancer susceptible strain prevented the subsequent development of breast tumours that castration performed between two and five months of age reduced but did not entirely prevent the development of tumours while castration after six months (i.e. after 30 oestrous cycles) had no effect on the subsequent incidence of tumours.

Murray (1928) confirmed the diminution of the incidence of breast cancer in mice following early gonadectomy or by enforced virginity and also showed that while intact or castrated males never developed breast tumours castrated males into whom ovaries had been grafted developed tumours in 7 per cent of cases.

(2) The experimental production of mammary carcinoma by oestrin

The discovery in 1929 of methods of preparing ovarian oestrogenic hormones in a pure form opened the way to more exact study of the problem of the association between ovarian activity and the genesis of cancer of the breast.

In 1932 and 1933 Lacassagne obtained mammary carcinomas in male and female mice by giving large weekly subcutaneous injections of oestrone benzoate. This result which was soon confirmed by Burrows (1935) and others (summarized by Cook *et al.* 1936 and by Cramer 1940) constitutes a major landmark in the history of cancer research for it affords the first discovered instance of a carcinogen of endogenous nature. In male mice treated with oestrin prior to the development of neoplasms the breasts show varying degrees of hyperplasia and cystic change closely resembling those of so-called chronic cystic mastitis in the human breast (Burrows, Bonser).

That the intrinsic susceptibility of mammary epithelium to neoplasia influences the production of tumours by oestrin was shown by the results of Lacassagne, Bonser and others. Thus, applying large doses of oestrone to male mice of cancer susceptible and cancer resistant strains Bonser observed carcinomas supervening on hyperplasia of ducts and acini in the former but only hyperplasia without carcinomas in the latter. On the other hand the same worker in later experiments (1937) succeeded in inducing mammary cancers in female mice of a strain not subject to the development of mammary tumours.

In an outline of the hormonal aetiology of breast cancer Cramer summarized experimental evidence which showed that the carcinogenic power of oestrin for mammary tissue was augmented by the adreno-cortical hormone and antagonized by the anterior pituitary thyrotropic hormone by an adrenal medullary hormone and by the male sex hormone, testosterone.

Observations of the pathological effects of oestrin overdosage on the mammary tissue of animals other than mice are so far few Heim (1937) after giving an account of a spontaneous mammary carcinoma in a rabbit, a species which rarely develops such tumours, described the production of hyperplastic cystic and papillomatous changes in the breasts of old female rabbits by subcutaneous injections of antuitrin S and oestrin, but without carcinomatous changes even after prolonged treatment

(3) The oestrous cycle in relation to the incidence of mammary carcinoma

Since the incidence of spontaneous mammary carcinoma varies greatly in different strains of mice and since different strains also show marked variations in the oestrous cycle the possibility of there existing a relationship between these two called for investigation The work of Bonser (1935) and of Burns *et al* (1936) however has shown that there is no parallelism between any of the features of the oestrous cycle and the incidence of mammary tumours The high incidence of mammary cancer in certain inbred strains of mice is not accompanied by any noteworthy peculiarities of the sexual cycle, the infrequency of tumours in other strains obtains in spite of the stimulation of oestrin with each oestrous cycle during reproductive life As the experimental production of mammary carcinoma by Lacassagne and others has shown however, oestrin overdosage may cause tumours in even cancer resistant strains

(4) Reproductive overactivity, duct stasis and mammary cancer

That purely local as well as hormonal factors also operate in the causation of mammary tumours was shown by Bagg (1925 and 1936) In a strain of mice of low tumour incidence he obtained many tumours by rapid breeding accompanied by milk stasis achieved by either non suckling or by ligation of ducts Later (1939) Bagg working with Hagopian confirmed and extended his original results using rats In these animals also rapid breeding and the prevention of suckling markedly increased the incidence of mammary carcinoma fibro adenoma and adenoma and in some of the rats with mammary tumours pituitary adenoma, hyperplastic adrenal glands or uterine leiomyomas were also present In some of the animals several different kinds of mammary tumours coexisted Duct stasis was a prominent feature in these experiments as in Bagg's earlier ones, and the authors suggested that chemical irritation from retained secretions may have been the immediate cause of the tumours

Confirmatory of the influence of local injury to the mammary ducts in the causation of mammary cancer were the experiments of Fekete and Green (1936) Using a strain of mice in which 80 per cent of parous females developed mammary cancer equally upon the two sides these workers found that if the right sided nipples were touched with a hot wire, and the mice then allowed to breed 70 per cent of the tumours which later developed in the breasts were in the injured right sided organs

(5) The possible mechanism of production of experimental mammary tumours

It is possible that the production of mammary tumours by oestrin overdosage is brought about partly by local factors similar to those responsible for Bagg's

results Oestrin overdosage first produces hyperplastic and cystic changes resembling those of so called 'chronic mastitis' in the human subject and in the experimentally produced lesion as in the spontaneously occurring human one duct obstruction and retention of secretions are often prominent features. Perhaps then the mammary hyperplasia induced by oestrin is finally provoked to neoplasia by a chemical stimulus from these retained secretions as suggested by Bagg. Further, it is not impossible or even unlikely that this stimulus may be due to specific carcinogenic substances generated in the stagnant duct contents. The abundant creamy or pultaceous material often seen in dilated ducts in the human breast is rich in fatty and lipoidal substances and the slow degradation of these under suitable conditions might involve the formation of carcinogenic compounds related to those discussed in Section I of this chapter. A search for such substances in retained mammary secretions is needed.

(6) Heredity and nursing factors in mammary cancer

More than once we have already referred to the fact that different stocks of mice differ in the incidence of spontaneously occurring mammary carcinomas. By close inbreeding from mice of high cancer ancestry it was found possible to obtain strains with an extremely high incidence of breast tumours. In some strains 80 per cent or more of parous females developed tumours. On the other hand by close inbreeding from mice of cancer free ancestry a race of animals which rarely or never showed spontaneous breast tumours could be developed. Differences in the incidence of spontaneous mammary cancers in different inbred strains of animals were therefore interpreted as dependent on hereditary factors which it was assumed determined differences in the susceptibility of the mammary epithelium to cancer evoking stimuli. A surprising fact which was soon apparent however was that maternal influences were more important than paternal in the transmission of this susceptibility.

That the different susceptibilities or insusceptibilities of inbred mice to the development of mammary neoplasms do not reflect purely genetic differences was shown by the work of Bittner summarized by him in 1940, 1942 and 1944. This worker found that the incidence of breast cancer in mice was markedly influenced by the source of the milk on which they had been fed. Mice which had been suckled by females of a stock with a low incidence of breast cancer also showed a low incidence and vice versa. Thus in one experiment, while a control group of non fostered female mice of a high-cancer stock eventually developed breast cancer in 84 per cent of cases female mice of the same stock, but suckled by foster mothers of low-cancer stock, later developed tumours in only 7 per cent. Nursing had no such influence on the subsequent incidence of lung tumours. Bittner concluded that the development of breast cancer in high cancer strains of mice is probably due to a combination of three factors (a) a breast-cancer producing influence transmitted through the milk of mothers of cancerous stock, (b) an inherited genetic susceptibility to breast cancer and (c) a hormonal factor affecting the breast. He also believed the milk factor to be fully as important as the genetic factor in the causation of breast cancer. The nature of the milk transmitted influence whether an enzyme or a chemical agent or a virus, remains undetermined, but it is known to be present, not only in

the milk, but in tumour tissue and other tissues of high cancer mice, and to retain its potency in filtrates and in desiccated or glycerinated tissue (For further details regarding the mammary tumours of mice and their experimental study, see the Symposium by the Staff of the National Cancer Institute, Washington, 1945)

SECTION V

THE HORMONAL PRODUCTION OF TUMOURS OTHER THAN MAMMARY

The experimental production of mammary tumours by oestrin was followed by reports of the production of tumours of other endocrine or endocrine controlled tissues by similar means. Although the experiments are so far few, the results are of great interest and show that an important new field of research has been opened up. Following oestrin overdosage, true tumours or tumour like proliferations have been observed in many organs, notably the testis, uterus, pituitary gland, prostate and thymus (For additional details, consult Burrows's book on sex hormones, 1945)

(a) *The testis*

Following the observation of Burrows (1935) that hyperplasia of the interstitial cells of the mouse's testis resulted from the administration of oestrogens, Bonser and Robson (1940), Bonser (1942 and 1944) and Hooker and Pfeiffer (1942) obtained true interstitial cell tumours in mice by this means. Although initially innocent and closely resembling spontaneously occurring interstitial cell tumours in animals and man, some of these growths eventually displayed malignant characters and produced metastases. The incidence of testicular tumours resulting from oestrinization varies with the strain of mice used, it is not affected by foster nursing and there is no parallelism between the number of testicular and mammary tumours produced (Bonser, 1944)

(b) *The uterus*

Of the many reports of cancerous or pre cancerous changes in the uterus following prolonged over-oestrinization the most notable are those of Gardner *et al* (1938), Suntzeff *et al* (1938) Pierson (1938) and Allen and Gardner (1941). The principal changes reported have been proliferation and squamous metaplasia of the uterine glands and their deep penetration into the muscle mainly in the cervical region. In some instances these changes may not have been neoplastic but rather extravagant hyperplasias of the nature of endometriosis but in other cases e.g. those of Allen and Gardner, there is little doubt that they were true tumours. Much more work is needed to elucidate the part played by hormones in the genesis of uterine carcinomas and the factors determining the transition from hyperplasia to neoplasia.

Lipschutz and co workers have published many papers on the production of multiple "fibroids" of the uterus and of the extra genital peritoneal tissues in guinea pigs following prolonged administration of oestrogens. Although large growths were obtained their neoplastic characters are open to doubt since they retrogressed on cessation of treatment. Nelson also observed fibromyomas of the uterus in oestrinized guinea pigs.

(c) The pituitary

Cramer and Horning (1936), Burrows (1936), Zondek (1938) and others have observed large tumour-like overgrowths of the anterior pituitary in mice or rats following prolonged administration of oestrogens. Proof of the truly neoplastic character of these will depend on showing that they continue to grow progressively after cessation of treatment.

(d) Other tissues

Cramer (1940) mentioned examples of carcinoma of the prostate and tumours of the thymus seen in oestrinized animals. Burrows's studies of the hyperplasia and metaplasia induced in the prostate by oestrin should be recalled. It remains for future research to ascertain if, and under what conditions, hormonal disturbances may be provocative of true tumours in tissues which like the prostate, are under hormonal influences or in the various endocrine tissues themselves. An important warning regarding the experimental hormonal production of tumours must be added here: in many of the experiments cited above the hormone dosages were relatively enormous, so that applicability of the results in human pathology must be assessed with due caution. However that the results are of significance especially as pointers to lines of future experimental and endocrinological research cannot be doubted.

SECTION VI

THE EXPERIMENTAL PRODUCTION OF TUMOURS OF THE LUNGS

In Section I we have already described the increased incidence of tumours of the lungs in mice after the administration of carcinogens by various routes. This is attributed to absorption into the circulation and carriage of these substances to the lungs by that route. While we must not overlook the possibility of such remote action in the causation of lung cancer it is clearly important to ascertain whether lung tumours can be produced by the direct inhalation of carcinogenic substances in the form of dusts, smokes or gases. Many experiments of this kind have been performed using soots, bituminous smokes, tobacco smoke, exhaust gases from internal combustion engines, powdered pitch, dusts from tarred roads, silicious and metallic dusts, radio active dusts, and pure carcinogenic hydrocarbons in powdered form.

(1) Experiment with soots, smokes or exhaust gases

These experiments, typical of which have been those of Schmidtman (1930), Schnurer and Hrythorn (1937) and Seelig and Benignus (1936 and 1938), have given negative or equivocal results. Thus Seelig and Benignus in a first experiment appeared to obtain a significant increase of lung tumours in mice inhaling bituminous soot, but were unable to confirm this result using a dust composed of lamp black mixed with carcinogenic tar. Schnurer and Hrythorn obtained no lung tumours following exposure of animals to coal smoke, and Schmidtman had a similar negative result with the soot from a Diesel engine. The results with tobacco smoke also have been inconclusive, although tobacco tar has been

shown to be carcinogenic when applied to the skin (Flory, Roffo) Experimental work, then has so far failed to prove that soot and organic smokes play a part in the genesis of lung tumours. It is of course possible that further experiments, using more suitable smokes and longer times of exposure, may still yield significant results.

(2) Experiments with dusts from tarred roads

Of particular interest are the researches of Campbell (1934, 1937, 1939 and 1942) on the carcinogenic effect of inhaled dust from tarred roads. This worker found that prolonged exposure of mice to such dust greatly increased the incidence of lung tumours—in one of his experiments nearly tenfold. At the same time most of the dusted mice developed cancers of the skin, evidently due to the tar present in the dust, since tar extracted from the dust with benzene was carcinogenic. The tar was not the only component of the dust responsible for the production of lung tumours, however, since mice exposed to the tar free residual dust after benzene extraction still showed an increased incidence of lung tumours, though to not so great an extent as when the tar also was present. In subsequent experiments (1942) Campbell used dust obtained from the same road surface five years after it had been tarred. This dust was much less active than the earlier sample as regards the production of skin tumours, but it still caused a ninefold increase in tumours of the lungs. The deduction to be drawn from Campbell's results is that, while the tar component of road dust is one factor in increasing the incidence of lung tumours in dusted animals it is not the only, nor necessarily the most important, component. Attention must be given also to the inorganic constituents of the dust, which include silica, oxide of iron and aluminium oxide.

(3) Experiments with inorganic dusts

In his 1940 experiments, Campbell found that dusting with precipitated silica or with iron oxide trebled the incidence of lung tumours in mice living ten months or longer. Subsequent experiments (1942) confirmed the carcinogenic effect of dusts containing silica and oxide of iron, and also demonstrated that steel grindings had some potency. Experiments carried out with radio active uranium-rich dust from the Joachimsthal mine gave a decided increase in lung tumours, though not strikingly greater than with some of the other dusts tested. Campbell pointed out that the prevalent view that lung cancer in the Schneeberg and Joachimsthal miners is due to radio active substances is still unconfirmed experimentally, other factors may be involved as well.

(4) Conclusion

Campbell's researches point clearly to the importance of inhaled substances in the genesis of lung tumours. It is for future experimental research to make more precise our knowledge of the carcinogenic activity of various occupational and other dusts inhaled by human beings, and to determine the particular ingredients of these which are mainly responsible. Enough has already been done to show that both organic and inorganic substances will be incriminated, and to indicate the methods to be pursued in research in this field. In addition, the

that such a substance is formed from the cholesterol in irradiated skin. However there is no conclusive evidence of this, Bergman *et al* found no carcinogenic activity in irradiated cholesterol applied to the skin of mice.

Hueper drew attention to the great variety of structure displayed by actinic carcinomas of the skin of rats.

(2) The experimental production of tumours by X-rays

Röntgen's discovery in 1895 was soon followed by the appearance of cases of chronic X ray dermatitis in exposed persons, and examples of supervening carcinoma of the skin began to be reported from 1902 onwards (references by Hueper). Experimental confirmation of the carcinogenic effects of X ray irradiation has been made by several workers notably Schurch (1930) who carried out a detailed histological study of all stages of the development of carcinomas of the ears of rabbits exposed for long periods to X rays. In these experiments, as in their human counterparts, tumours have usually appeared only after relatively long periods of exposure, for example in Schurch's rabbits two years or longer.

The occasional development of sarcomas in persons over exposed to X rays, usually following Röntgen treatment of tuberculous lesions (Hueper, 1942) has also been paralleled experimentally. As long ago as 1909, Marie and co-workers obtained a spindle celled sarcoma in the rat's cutis after prolonged irradiation, a result repeated by Bauer in 1937. Lacassagne and Vinzent (1928 and 1929), Burrows and co-workers (1937) and Burrows and Clarkson (1943) obtained sarcomas of tissues which had been made the site of chronic inflammation artificially. The English workers produced subcutaneous spindle celled growths by irradiating the site of injections of silica and kaolin. Chronic inflammatory tissue is thus more susceptible than normal connective tissue to the development of sarcomas following exposure to X rays.

(3) The experimental production of tumours by radio active substances

Most of the tumours produced by radio active substances, either in man or experimental animals, have been sarcomas, but a few carcinomas of the skin undoubtedly due to radium have been reported.

The first recognized instances of human sarcomas due to radio active materials were the occupational sarcomas of bone due to radium and mesothorium absorbed by workers using luminous paints. The remarkable story of this occupational tumour reported first by Martland and Humphries in 1929 and later by Martland, will be fully described in Chapter 43. No occupational sarcomas in soft tissues due to radio active substances have so far been reported, but Norgaard described an instance of fibrosarcoma of the tibia due to intra articular injections of radium chloride for therapeutic purposes.

Experimental sarcomas of soft tissues and of bones have been produced by many workers by means of radio active substances. Daels (1926) and Daels and Biltz (1931) obtained subcutaneous sarcomas in rats and mice following the introduction of small amounts of radium salts in glass tubes. Ross confirmed this, using radium adequately screened in platinum, thus proving the sarcoma evoking power of pure gamma rays. Sabin and co-workers obtained osteogenic sarcomas in 2 of 7 surviving rabbits following repeated intravenous injections of radium and mesothorium, thus establishing the experimental counterpart of the occupational

sarcomas of workers with radio active paints Schurch and Uehlinger reported the frequent development of sarcomas following the direct introduction of radium and mesothorium into the femurs of rabbits Dunlap *et al* (1944) obtained transplantable osteogenic sarcomas by feeding rats with radium

In view of the use of Thorotrast (colloidal thorium dioxide) in radiodiagnosis the ready experimental production of sarcomas by subcutaneous or intraperitoneal injections of this substance is of special interest (Roussy *et al* Selbie, and Foulds) While no tumours following the use of Thorotrast in man have yet been recorded the risk that such may appear during the next decade or more when due time has elapsed following the use of this relatively recent method of diagnosis, must be recognized It is noteworthy that not only sarcoma, but also carcinoma, may be caused by this substance, in one of Foulds's guinea pigs, which received injections into the base of the nipple, a transplantable mammary carcinoma with metastases developed

SECTION VIII

PARASITES AS CARCINOGENIC AGENTS

The student approaching the subject of tumour causation is perplexed by the diversity of opinions regarding the causative role of various parasites The views, once widely held that tumours were caused by specific protozoa or fungi, have long since been discarded, and although syphilitic glossitis clearly predisposes to carcinoma of the human tongue, and although tumours do sometimes supervene on various other chronic inflammatory lesions none of the ordinary pathogenic bacteria have been incriminated as carcinogenic As regards metazoal parasites doubt has been cast on the once widely accepted carcinogenic properties of the nematode called by Fibiger *Spiroptera neoplastica* but there is no doubt that some other parasites notably cysticercus in rats can induce true tumours Modern research has disclosed more elusive parasites filterable viruses which are responsible for certain special classes of tumours and the volume of published work in this still unsettled field has become disconcertingly great

(1) Fibiger's '*Spiroptera neoplastica*

In 1913 Fibiger described what he believed to be carcinomatous growths in the forestomach of rats infested with a small nematode, which was accordingly called *Spiroptera neoplastica* or *Gongylonema neoplasticum* The adult parasites reside in the stratified epithelial mucosa of the tongue oesophagus and fore stomach Ova discharged in the faeces and eaten by a certain species of cockroach reach and become encysted in the striated muscles of this intermediate host The cycle of development of the parasite is completed when rats eat infected cockroaches Heavy infestation of the rat's forestomach produces huge multiple papillary epithelial overgrowths According to Fibiger these growths in his experiments eventually became malignant infiltrating the wall of the stomach and producing metastases in lymph glands and lungs Fibiger also reported cancers of tongues infested by the parasite

Although Fibiger's results were widely accepted as the first experimental

production of malignant tumours, his interpretation is open to doubt. As long ago as 1918, Bullock and Rohdenburg showed that carcinoma like papillary overgrowth of the rat's stomach could be easily induced by simple mechanical injury and that squamous metaplasia in bronchial epithelium in the very frequent chronic broncho pneumonia affecting rats may produce pictures similar to those of the suspected pulmonary metastases in Fibiger's rats. They therefore questioned Fibiger's claim to have produced true tumours. Subsequent workers also have failed to obtain genuine tumours by means of the parasite, and Passey *et al* advanced evidence that the epithelial overgrowth in Fibiger's rats was partly the result of vitamin deficiency, and that, as Bullock and Rohdenburg had suggested, the lung lesions thought by Fibiger to be metastatic growths may well have resulted from bronchiectasis and metaplasia.

(2) *Cysticercus* sarcoma of the rat's liver

Following the papers of Bullock and Rohdenburg (1916 and 1917) on the association of parasitic cysts with sarcomas of the rat's liver, Bullock and Curtis (1925) used the parasite for producing these tumours experimentally. The parasite *Cysticercus fasciolaris*, is the cystic form of the cat tapeworm, *Taenia crassicollis*, and by feeding rats with the eggs of this worm, Bullock and Curtis obtained single or multiple tumours of the livers of 1400 rats. The sarcomas developed from the connective tissue walls around the cysts, the main types were spindle celled or polymorphous celled, but there were some fibrosarcomas, one liposarcoma, and cartilaginous tissue was present in several tumours, one of which showed cartilage also in its peritoneal metastases.

(3) The Rous sarcoma and other filterable tumours of birds

Since their first discovery in 1910, these peculiar tumours have been the subject of intensive research producing an enormous volume of papers. Only the barest outline can be attempted here, for further details the reader should consult the excellent review by Foulds (1934) and the papers of Rous and co-workers (references by Rous 1935).

In 1910 Rous found that a transplantable sarcoma of the domestic fowl, now known as 'Rous sarcoma I', could be transmitted by cell free filtrates. Other distinct fowl sarcomas similarly transmissible were soon discovered. These differ decidedly from one another in both histological structure and behaviour, and there is general agreement that the filterable agents responsible for them are distinct and will evoke only growths of the same kind as those from which they are derived. It is therefore improper to speak of all filterable tumours as "Rous sarcomas", this obscures the differences between the several tumours.

In transmission by grafts the resulting tumours appear clearly to be derived wholly or predominantly from the implanted cells, but in cell free transmission the tumours arise of course from the cells of the new host. The precise histogenesis of the filterable tumours, whether they arise mainly from fibroblasts, monocytes or fixed endothelial cells, is controversial and is perhaps not material in view of the probable intermutability of these allied mesenchymal cells. Certain it is that all of the tumours are sarcomatous, none of the known epithelial tumours of birds has proved to be filterable.

Filtrates differ greatly, and often unaccountably in potency. The more malignant growths, such as Rous sarcoma I, usually yield active filtrates but filtrates of the less malignant tumours are often inactive. Even sarcoma I filtrates may be obstinately inactive for a period, and then filterability may spontaneously return. The susceptibilities of the agents to antiseptics and heat resemble those of living agents but they appear to have a high resistance to ultra violet rays, X rays and radio active substances. Ultrafiltration centrifugation and electron microscopy show that the agents are particulate, and that the mean size of Rous sarcoma I particles is about 50μ . During the growth of a tumour there is a concomitant increase in quantity of the agent.

Much interesting work has been done on the antigenic properties of the filterable agents, but interpretation of the results is still debatable on many points. One remarkable observation, recorded by Amies and co workers (1940), must be mentioned. Rous agent is neutralized not only by the serum of rabbits treated with the agent itself as antigen, but also by the serum of rabbits treated with normal fowl serum or tissues as antigen and, both anti agent and anti fowl sera are deprived of their neutralizing properties by contact with normal chicken embryo. Hence the agent of Rous sarcoma I appears to contain in addition to a specific antigen a second antigen also present in fowl tissue a relationship quite peculiar in virus serology.

Tumour producing activity has often been demonstrated in the blood or other body fluids of tumour bearing birds and it has been found that the agent may be localized from the blood stream and may produce secondary tumours in injured or inflamed tissues. Yet it is certain that spontaneous metastases usually do not arise in this way, but result from embolic dissemination of tumour cells as with mammalian tumours. There is no evidence that the tumours are infectious normal fowls do not develop tumours when kept with tumour bearing birds or when fed with tumour tissue.

The transmissible leucoses of fowls are clearly closely related to the filterable tumours they can be transmitted by cell free material and they may occur in association with sarcomatous tumours.

With rare exceptions sarcomas induced in fowls by chemical carcinogens have proved to be non filterable. The few instances in which filterable tumours have occurred are of uncertain explanation accidental contamination of the injected carcinogen by agent may have been responsible. Further work is needed in this field.

Have the filterable tumours of birds any bearing on the causation of mammalian tumours? In spite of much debate this question is still unanswered. To those who incline to the virus hypothesis of tumour causation in general the filterable tumours appear as a prototype and as the most favourable material for elucidation of the problems of causation and they explain the failure to demonstrate filterability in mammalian tumours as due to permanent inactivation or masking of the responsible agents in filtrates just as Rous sarcoma filtrates may show unaccountable phases of inactivity. Those however who see much of occupational cancer in man or of experimental chemical carcinogens are more likely to regard the filterable tumours as probably constituting a quite special class of diseases peculiar to birds. Certain it is (a) that the filterable avian agents differ from all

other carcinogenic agents in that they can induce only the precise kinds of tumours as those from which they came, and that they multiply in the tumours which they originate, and (b) that these agents are demonstrable only in certain tumours of mesenchymal tissues and never in epithelial tumours in birds

(4) The Shope tumour of rabbits

In 1933 Shope and Hurst found that papillomas of the skin of the cotton tail rabbit were transmissible by cell free filtrates or by glycerinated tissue to both cotton tail and domestic rabbits. The papillomas so produced grew to large cauliflower like masses. The tumours could be passaged repeatedly in cotton tails but only one or two passages could be made in ordinary rabbits. In the cotton tail the papillomas rarely become malignant, but in the domestic rabbit they frequently become carcinomatous within two years (Gvc, 1938). Of great interest is the fact that filtrates of the carcinomatous tissue are inactive. Rous found, however, that successful transplantation of carcinomatous tissue, apparently devoid of virus, to fresh host rabbits was followed by the appearance in their sera of an immune body which neutralized papilloma virus. This result suggested that the carcinomatous tissue, though incapable of yielding active filtrates, nevertheless contained the virus in a masked or inactive form. Further elucidation of this problem is needed. A valuable account of the Shope tumour was given by Rous in his Harvey lecture in 1935.

Experiments by Rous on the combined effect of Shope virus and a chemical carcinogen are of interest. It was found that if rabbits were painted with tar until papillomas began to appear, and were then given intravenous injections of Shope virus active papillomas or carcinomas developed in the tarred areas much more quickly than in control tarred animals which had received no virus. This result suggested that the chemical carcinogen had conditioned the tissue for reception of the virus which then precipitated the neoplastic change. Rous and Friedwald found that chemical carcinogens caused rapid cancerous change in Shope papillomas.

Whether deductions drawn from the behaviour of the Shope tumour and its virus are applicable to mammalian tumours generally, only future research can decide. So far, the evidence would suggest that this tumour is a peculiar one, and that no hasty conclusions regarding tumour causation in general should be drawn from it.

Stanley has found that the Shope virus is a macromolecular protein which can be isolated in a crystalline form and he regards it as a pathological protein formed autocatalytically within the cells.

(5) Lucke's adenocarcinoma of the frog's kidney

In his interesting studies of renal adenocarcinomas of frogs, Lucke observed acidophil intra nuclear inclusions which suggest of a virus. Experiments showed that inoculations of tumour tissue or with desiccated or glycerinated development of characteristic renal tumours in 20 per a percentage much higher than in control. No tumours of inoculation and no tumours in control.

frogs, Lucke prepared with living tissue and by an artificial method. The results of the experiments are as follows:

concluded that his tumour is probably due to "an inclusion forming, organ-specific virus

SECTION IX

ENDOGENOUS CHEMICAL CARCINOGENS

The close chemical relationship between the carcinogenic hydrocarbons of the benzanthracene group and some naturally occurring biological substances such as the bile acids and the sterols has naturally led to speculation as to the possible formation of carcinogens in the tissues themselves. It is quite feasible that in suitable pathological conditions, abnormal metabolic or degenerative products may include carcinogenic substances. I have already mentioned the possibility that this may occur in the contents of obstructed breast ducts and it is not difficult to think of other possible instances. Perhaps in the gall stones which are usually present in the cancerous gall bladder a carcinogenic substance has been slowly generated perhaps this has happened also in the smegma retained under the prepuce of the cancerous penis, perhaps the sebaceous contents of a cystic teratoma of the ovary in which carcinoma has supervened has developed carcinogenic properties perhaps the proneness to malignant change following syphilis of the tongue or cysticercus infection of the liver is due to carcinogenic metabolic products peculiar to those inflammations.

The research of the future will certainly include attempts to isolate pure carcinogenic substances from these and other conditions. While no such endogenous carcinogens have so far been identified, there is already substantial experimental evidence of their existence. For example it has been found that suitable extracts of normal or of diseased livers are feebly carcinogenic (see Kleinenberg *et al.*, 1940 and 1941) and that this property is more pronounced in extracts of livers of cancerous patients and in extracts of livers of races unusually liable to hepatic cancer—for example the African Bantus (des Ligneris, 1940; Hieger 1940; Steiner 1942). Recall here also the discovery of Kennaway and co workers that under certain conditions desoxycholic acid may be carcinogenic.

REFERENCES

For main references and reviews the author's name is in capitals and the full title is given. Some minor references given in the text, but not specified in the following list will be found readily from the appropriate main references.

GENERAL

- BAUFR K H (1937) Referat über Berufsschaden und Krebs. *Verh Dtsch path Ges*, 30 239.
- COOK J W, HASLEWOOD C A D, HILWETT C L, HIEGER I, KENNAWAY E L and MAYNARD W V (1937) Chemical compounds as carcinogenic agents. *Amer J Cancer* 29 219.
- COOK J W, and KENNAWAY E L (1938 and 1940) Chemical compounds as carcinogenic agents. *Amer J Cancer* 1938 33 50 19-40 39 381 and 521.
- HUTHER W C (1942) *Occupational Tumors and Allied Diseases*. Springfield U.S.A.
- KENNAWAY E L and KENNAWAY S M (1937) Some factors affecting carcinogenesis. *Acta Internat. Union against Cancer* 2 101.
- ROSS H C (1918) Occupational cancer. *J Cancer Res* 3 321.
- STALMUEHR M (1937) Referat über Beruf und Krebs. *Verh Dtsch path Ges* 30 188.

WILLIS, R A (1945) An outline of recent advances in the experimental production of tumours *Med J Austral* 1 361

HYDROCARBONS

BADGER, G M, COOK, J W, HEWETT, C L, KENNAWAY, E L, KLNNAWAY, N M, MARTIN, R H, and ROBINSON, A M (1940 and 1942) 'The Production of cancer by pure hydrocarbons' *Proc Roy Soc B* 1940 129 439 1942 131 170

BARRY, G, COOK, J W, HASLEWOOD, G A D, HEWETT, C L, HIEGER, I, and KENNAWAY, E L (1935) The Production of cancer by pure hydrocarbons *Proc Roy Soc B* 117 318

Barry G and Cook J W (1934) *Amer J Cancer* 20 58

Beck S and Peacock P R (1941) *Brit Med J* 1, 81

Berenblum I (1941) *Cancer Res* 1 807

BONSER, G M (1938) The Hereditary factor in induced skin tumours in mice, *J Path Bact* 46 581

BONSER, G M, and ORR, J W (1939) The Morphology of 160 tumours induced by carcinogenic hydrocarbons in the subcutaneous tissues of mice', *J Path Bact* 49 171

Bonsler G M (1940) *Amer J Cancer* 38 319

Boyland E and Burrows H (1935) *J Path Bact* 41 231

Bradbury J T, Bachmann W E and Lewisohn M G (1941) *Cancer Res*, 1 685

BROCKBANK, E M (1941) *Mule Spinner's Cancer Epithelioma of the Skin in Cotton Spinners* London

Brues A M and Marble B B (1939) *Amer J Cancer* 37 45

Brunschwig A and Bissell A D (1938) *Arch Surg* 36 53

Brunschwig A and Rasmussen R A (1941) *Cancer Res* 1 371

BURROWS, H, HIEGER, I, and KENNAWAY, E L (1932) The Experimental production of tumours of connective tissue *Amer J Cancer* 16 57

Burrows H and Boyland E (1938) *Amer J Cancer* 32 367

COWDRY, E V and PALFITA, F X (1941) Changes in cellular nuclear and nucleolar sizes during methylcholanthrene epidermal carcinogenesis *J Nat Cancer Inst* 1 745

Crabtree H G (1940) *J Path Bact* 51 299 and 303

Crabtree H G (1943) *Imp Cancer Res Fund Sci Rep*

Deelman H T (1922 1923 and 1924) *Zeit Krebsforsch* 1922 18 261 1923 19 125 1924 21 220

Doljanski L and Halberstaedter L (1937) *Amer J Cancer* 29 285

Earle W R and Voegtlin C (1938) *Amer J Cancer* 34 373

FILSER, L F, FIESER, M, HERSHBERG, E B, NEWMAN M S, SELIGMAN, A M, and SHEAR M J (1937) Carcinogenic activity of the cholanthrenes and of other I 2 benzanthracene derivatives *Amer J Cancer* 29 260

FIESER, L F (1938) Carcinogenic activity structure and chemical reactivity of polynuclear aromatic hydrocarbons *Amer J Cancer* 34 37

Furth J and Furth O B (1938) *Amer J Cancer* 34 169

Glucksmann A (1945) *Cancer Res* 5 385

Haagensen C D and Krehbiel O F (1936) *Amer J Cancer* 26 368

HIEGER, I (1930) The Spectra of cancer producing tars and oils and of related substances *Biochem J* 24 505

Iball J (1939) *Amer J Cancer* 35 188

Ilfield F W (1936) *Amer J Cancer* 26 743

KENNAWAY, E L (1930) Further experiments on cancer producing substances *Biochem J* 24 497

Lavick P S, Moore P R, Rusch H P and Baumann C A (1942) *Cancer Res* 2 189

Law L W (1941) *Amer J Path* 17 827

Law L W (1941) *Cancer Res* 1 564

Leitch A (1922) *Brit Med J* ii 1104

Lewis W H (1936) *Harvey Lectures* p 214

MACKENZIE, I and ROUS, P (1941) The Experimental disclosure of latent neoplastic changes in tarred skin *J Exp Med* 73 391

Magnus H A (1939) *J Path Bact* 49 21

Mider G B and Morton J J (1939) *Amer J Cancer* 37 355

- Morton J J (1941) *Surg Gyn Obst* 73 345
 Mottram J C (1941) *Cancer Res* 1 313
 Murphy J B and Sturm E (1925) *J Exp Med* 42 693
 Murray J A (1922) *Brit Med J* ii 1103
 Orr J W (1935) *Brit J Exp Path* 16 121
 Orr J W (1935 and 1937) *J Path Bact* 1935 41 51 1937 44 19
 ORR J W (1938) The Changes antecedent to tumour formation during the treatment of mouse skin with carcinogenic hydrocarbons *J Path Bact* 46 495
 ORR J W (1939) An investigation of the histological changes in the subcutaneous tissues of mice during the induction of sarcoma by carcinogenic hydrocarbons, *J Path Bact*, 49 157
 Orr J W (1943) *J Path Bact* 55 483
 Page R C (1938) *Arch Path* 26 800
 Passey R D (1934 and 1935) *Brit Emp Cancer Campaign Annual Rep*
 Passey R D (1938) *J Path Bact* 47 345
 Peacock P R (1933) *J Path Bact* 36 141
 Peacock P R (1936) *Brit J Exp Path* 17 164
 Peacock P R and Beck S (1938) *Brit J Exp Path* 19 315
 Peacock P R and Kirby A H M (1944) *Cancer Res* 4 88
 Peers J H (1940) *Amer J Path* 16 799
 PULLINGER B D (1940) The First effects on mouse skin of some polycyclic hydrocarbons *J Path Bact* 50 463
 Pullinger B D (1941 1943 and 1945) *J Path Bact* 1941 53 287 1943 55 301 1945 57, 467 and 477
 ROUS P and KIDD J G (1941) Conditional neoplasms and subthreshold neoplastic states *J Exp Med* 73 365
 SEELIG M G, and COOPER, Z. K. (1933) A review of the recent literature of tar cancer *Amer J Cancer* 17 589
 Seligman A M Shear M J and Alexander L (1939) *Amer J Cancer* 37 364
 Semproni A and Morelli E (1939) *Amer J Cancer* 35 534
 SHEAR M J (1936) The Production of tumors in mice by hydrocarbons *Amer J Cancer* 26 322
 SHEAR, M J (1938) Studies in carcinogenesis Methyl derivatives of 1 2 benzanthracene *Amer J Cancer* 33 499
 Shear M J (1939) *Amer J Cancer* 36 211
 SHIMKIN M B (1939) Production of lung tumors in mice by intratracheal administration of carcinogenic hydrocarbons *Amer J Cancer* 35 538
 Stewart H L and Andervont H B (1938) *Arch Path* 26 1009
 Twort J M and Twort C C (1936) *J Path Bact* 42 303
 Twort J M and Twort C C (1939) *Amer J Cancer* 35 80
 WOGLOM W H (1926) Experimental tar cancer *Arch Path* 2 533 and 708
 Yamagiwa K and Ichikawa K (1918) *J Cancer Res* 3 1
 Zimmerman H M and Arnold H (1941) *Cancer Res* 1 919

AZO-COMPOUNDS

- Cook J W Hewitt C L Kennaway E L and Kennaway N M (1940) *Amer J Cancer* 40 62
 Edwards J E (1941) *J Nat Cancer Inst* 2 197
 Kinoshita R (1937) *Trans Path Soc Jap* 27 665
 Miller J A and Baumann C A (1945) *Cancer Res* 5 227
 ORR J W (1940) The Histology of the rat's liver during the course of carcinogenesis by butter yellow (*p*-dimethyl aminoazobenzene) *J Path Bact* 50 393
 Sasaki T and Yoshida T (1935) *Virchows Arch* 295 175
 SHEAR M J (1937) Development of liver tumors in pure strain mice following the injection of 2 amino-5 azotoluene *Amer J Cancer* 29 269
 Sugiyama K, Halter C R, Kensler C J and Rhoads C P (1945) *Cancer Res* 5 235

OTHER CHEMICAL CARCINOGENS

- Armstrong E C and Bonser G M (1944) *J Path Bact* 56 507
 Berenblum I and Bonser G M (1937) *J Indust Hyg and Toxicol* 19 86
 Bielschowsky F (1944 1945 and 1946) *Brit J Exp Path*, 1944, 25 1, 1945 26 270, 1946, 27 54 and 135
 Bielschowsky F and Green H N (1945) *Nature* 156 780
 Bonser G M (1943) *J Path Bact* 55 1
 Browning C H Gulbrandsen R and Niven J S F (1936) *J Path Bact* 42 155
 Burrows H (1936) *J Path Bact* 43 427
 HARTWELL, J L Survey of compounds which have been tested for carcinogenic activity (National Cancer Institute)
 Hueper W C Wiley F H and Wolfe H D (1938) *J Indust Hyg and Toxicol* 20 46
 Hueper W C (1942) *Cancer Res* 2 551
 Letch A and Kennaway E L (1922) *Brit Med J* 11 1107
 Narat J K (1925) *J Cancer Res* 9 135
 Staemmler M (1935) *Virchows Arch* 295 366
 Wilson R H De Eds F and Cox A J (1941) *Cancer Res* 1 595

EXPERIMENTAL MAMMARY TUMOURS

- Bagg H J (1925) *J Cancer Res* 9 498
 Bagg H J (1936) *Amer J Cancer* 27 542
 Bagg H J and Hagopian F (1939) *Amer J Cancer* 35 175
 BITTNER, J J (1940) Breast cancer in mice as influenced by nursing *J Nat Cancer Inst* 1 155
 BITTNER J J (1942) Possible relationship of the estrogenic hormones genetic susceptibility and milk influence in the production of mammary cancer in mice *Cancer Res* 2 710
 Bittner J J (1944) *Cancer Res* 4 159
 Bonser G M (1935 and 1936) *J Path Bact* 1935 41 33 1936 42 169
 Burns I L Moskop M Sontzoff V and Loeb L (1936) *Amer J Cancer* 26 56
 BURROWS H (1935) Pathological changes induced in the mamma by oestrogenic compounds *Brit J Surg* 23 191
 CRAMER W (1940) The Hormonal etiology of breast cancer *Amer J Cancer* 38 463
 Heiman J (1937) *Amer J Cancer* 29 93
 Lacassagne A (1932) *CR Acad Sci* 195 630
 Lacassagne A (1933) *CR Soc Biol* 114 427
 Lathrop A E C and Loeb L (1916) *J Cancer Res* 1 1
 Murray W S (1928) *J Cancer Res* 12 18
 National Cancer Institute Staff (1945) *Symposium on Mammary Tumours in Mice* Washington

OTHER EXPERIMENTAL TUMOURS PRODUCED BY HORMONES

- Allen F and Gardner W U (1941) *Cancer Res* 1 359
 Bonser G M and Robson J M (1940) *J Path Bact* 51 9
 Bonser G M (1942 and 1944) *J Path Bact* 1942 54 149 1944 56 15
 Burrows H (1935) *J Path Bact* 41 218
 Burrows H (1936) *Amer J Cancer* 28 741
 Burrows H (1945) *Biological Actions of Sex Hormones* Cambridge
 Cramer W and Horning E S (1936) *Lancet* 1 247
 Cramer W (1940) *Amer J Cancer* 38 463
 Gardner W U Allen E Smith G M and Strong L C (1938) *J Amer Med Assoc* 110 1182
 Hooker C W and Pfeiffer C A (1942) *Cancer Res* 2 759
 Lipschutz A and Vargas L (1941) *Cancer Res* 1 236
 Nelson W O (1939) *Endocrinology* 24 50
 Pierson H (1938) *Zeit Krebsforsch* 47 1 and 336
 Zondek B (1938) *Amer J Cancer* 33 555

EXPERIMENTAL TUMOURS OF THE LUNGS

- Campbell J A (1940 1942 and 1943) *Brit Med J* 1940 11 275 1942 1 217 1943 1 179

- Flory C M (1941) *Cancer Res* 1 262
 Roffo A H (1939) *Zeit Krebsforsch* 49 588
 Schmidtman M (1930) *Zeit Krebsforsch* 32 677
 Schnurer L and Haythorn S (1937) *Amer J Path* 13 799
 Seelig M G and Benignus E L (1938) *Amer J Cancer* 34 391

RADIATIONS AS CARCINOGENIC AGENTS

- Beard H H Bogess T S and Von Hamm E (1936) *Amer J Cancer* 27 257
 Bergmann W Stavely H E Strong L C and Smith G M (1940) *Amer J Cancer* 38 81
 Burrows H Mayneord W V and Roberts J E (1937) *Proc Roy Soc B* 123 213
 Burrows H and Clarkson J R (1943) *Brit J Radiol* 16 381
 Daels F and Biltris R (1931) *Bull Assoc franç Cancer* 20 32
 Doniach J and Mottram J C (1940) *Amer J Cancer* 39 234
 Dunlap C E Aub J C Evans R D and Harris R S (1944) *Amer J Path* 20 1
 Findlay G M (1928 and 1930) *Lancet* 1928 ii 1070 1930 i 1229
 Foulds L (1939) *Amer J Cancer* 35 363
 Lacassagne A and Vincent R (1929) *C R Soc Biol* 100 249
 Martland H S (1931) *Amer J Cancer* 15 2435
 Norgaard F (1939) *Amer J Cancer* 37 329
 Ross J M (1936) *J Path Bact* 43 267
 Rusch H P and Baumann C A (1939) *Amer J Cancer* 35 55
 Rusch H P Kline B E and Baumann C A (1941) *Arch Path* 31 135 and (1942) *Cancer Res* 2 183
 Sabin F R Doan C A and Forkner C E (1932) *J Exp Med* 56 267
 Schurch O (1930) *Zeit Krebsforsch* 32 449 and 33 1
 Schurch O and Uehlinger E (1935) *Arch klin Chir* 183 704

PARASITES AS CARCINOGENIC AGENTS

- Amies C R *et al* Cited by Haddow (1944) *Nature* 154 194
 Bullock F D and Rohdenburg G L (1917) *J Cancer Res* 2 39
 BULLOCK F D and ROHDENBURG G L (1918) Experimental carcinomata of animals and their relation to true malignant tumors *J Cancer Res* 3 227 (A classical paper urging caution in the interpretation of the results of experiments in carcinogenesis)
 BULLOCK F D and CURTIS M R (1925) Types of cysticercus tumors *J Cancer Res* 9 425
 Fibiger J (1913 and 1914) *Zeit Krebsforsch* 1913 13 217 1914 14 295
 FOULDS L (1934) The filterable tumours of fowls a critical review *Imp Cancer Res Fund Ser Rep (Suppl)* (Gives a full reference list of earlier literature)
 Gye W E (1938) *Brit Med J* 1 551
 Lucké B (1938) *J Exp Med* 68 457
 Passey R D Leese A and Knox J C (1936) *J Path Bact* 42 425
 Rohdenburg G L and Bullock F D (1916) *J Cancer Res* 1 87
 ROUS P (1935) *The Virus Tumors and the Tumor Problem* Harvey Lectures p 74
 Rous P and Beard J W (1935) *J Exp Med* 62 523
 Rous P Kidd J G and Beard J W (1936) *J Exp Med* 64 385 and 401
 Rous P and Friedewald W F (1944) *J Exp Med* 79 511
 Shope R E and Hurst E W (1933) *J Exp Med* 58 607
 Stanley W M (1939) *Physiol Rev* 19 524

ENDOGENOUS CARCINOGENS

- Hieger I (1940) *Amer J Cancer* 39 496
 KLEINFELDER H E NEUFACH S A and SHABAD L M (1940) Endogenic blastogenic substances *Amer J Cancer* 39 463 and (1941) *Cancer Res* 1 853
 des Ligneris M J A (1940) *Amer J Cancer* 39 459
 Steiner P (1942) *Cancer Res* 2 425

CHAPTER 5

THE STATISTICAL STUDY OF TUMOURS

THE MOST voluminous, and in general least reliable, of the main sections of the literature on neoplasms is the statistical. A spate of papers flows unceasingly into a hundred journals and its very bulk prohibits its piecemeal assimilation. Fortunately, however, by the application of certain simple tests of reliability, much of it can be dismissed at a glance. This chapter is concerned, therefore, not with a minute critical analysis of many published papers, but with the formulation of some general rules regarding the degree of reliability of cancer statistics of various kinds.

I advise the reader to whom the subject is not familiar to read Bashford's and Murray's classical critique (1905), and to study the excellent papers of Wells (1927 and 1931) and Cramer (1937), the one stressing the many sources of error in cancer statistics, the other indicating the ways in which statistical research rightly prosecuted, has been and might be of value. Hill's valuable book (1939) on medical statistics especially Chapters 14-16 on common fallacies, should also be read.

' CANCER ' AN ILL DEFINED HETEROGENEOUS GROUP OF DISEASES

Many statistical writers discuss "cancer" as a whole, tacitly ignoring the vague meaning of this word and the great variety of diseases it embraces. Most of such writers clearly use cancer as synonymous for all kinds of malignant tumours. But as shown in Chapter 3, the distinction between "innocence" and "malignancy" is an indefinite and arbitrary one, almost every histogenetic group of neoplasms displaying a range of behaviour from "benign" to "malignant". Gliomas, basal cell epitheliomas of the skin, the so-called "mixed" salivary tumours, many of the papillary growths of the bladder, ganglioneuromas, are examples of neoplasms which might be, and indeed have been, included under the term "cancer" by some writers and excluded by others. To have biological validity, statistical studies purporting to embrace "cancer" as a whole should include *all* tumours. To restrict such studies to those tumours only which have been labelled "malignant" in clinical records or on death certificates is to commit the statistical crime of making an arbitrary selection of part only of the relevant material.

But further, to discuss cancer as a whole even if this term were clearly definable, would have little value. "Cancer" embraces fully as many and as diverse entities as 'inflammation' and statisticians have, rightly, not deemed it useful to make analyses of inflammatory diseases as a whole. To lump together for statistical study a heterogeneous collection of tumours containing such different diseases as gliomas of the brain, carcinomas of the stomach and teratomas of the testis is no more sensible than it would be to lump together a heterogeneous collection of bacterial inflammations containing such diverse diseases as erysipelas, typhoid fever and tuberculosis.

Clearly statistical analysis can be applied usefully only to well defined homogeneous groups or species of tumours. If reliable figures can be established for these, then any appropriate summations of these figures which may be deemed

useful can be made. Cramer emphasizes the necessity of recording the data for the incidence of cancer in man separately for each tissue or organ. Sweeping statements about cancer in general, without clear specification of the constituents included and evidence of the degree of reliability of the figures for each constituent, are valueless. At the present time, we *cannot* have reliable figures of the frequency and trend of 'cancer' as a whole because, as will be shown below, available estimates regarding many of the major constituent groups of tumours are widely inaccurate.

DEGREE OF ACCURACY OF DIAGNOSIS

It is an axiom that the prerequisite of any statistical investigation is accuracy of the primary data. Principal of the primary data in tumour statistics are the pathological diagnoses of the cases studied. If any considerable proportion of these are erroneous or uncertain then the entire research is vitiated at its outset. Application of this basic principle will result in prompt rejection of many published statistical studies. When a writer fails to specify clearly the nature of his material, the bases of the diagnoses made, and the degree of diagnostic accuracy attained, it is a waste of time to study his analyses further.

The fundamental data of statistical cancer research—the diagnoses made by clinicians and pathologists—have very diverse degrees of accuracy. There are four ascending grades of diagnostic precision:

Grade 1 Diagnosis by simple physical examination only

Grade 2 Diagnosis by physical examination supplemented by special methods

Grade 3 Diagnosis by histological examination of surgically removed tissues

Grade 4 Diagnosis by necropsy, (a) without histological confirmation
(b) with histological confirmation

These grades of accuracy are of the first importance in assessing the reliability of any series of cases examined statistically and their meaning and importance must be made clear.

Grade 1

Grade 1 comprises diagnoses made by practitioners from simple physical examination of the patients, without resort to special diagnostic methods—pathological, radiological, endoscopic or operative. Many diagnoses made by general practitioners, and appearing on death certificates fall into this class. Their degree of reliability is very variable, often low, and in any case incapable of assessment, varying with the ability and experience of the practitioner, the nature of the disease and the nature of the community. The purely clinical diagnosis of external cancers, e.g. carcinoma of the breast or of the lip, is much more reliable than that of internal cancers, e.g. carcinoma of the stomach or of the lung. Some quite common internal tumours are so difficult to diagnose by simple physical examination that many general practitioners think of them erroneously as rarities, e.g. carcinoma of the lung, cerebral glioma. Except when they are more fully investigated by specialists, very few of these tumours are diagnosed correctly, and the supposedly increased frequency of such tumours during recent years is undoubtedly due largely to increasing recognition by

practitioners of the need for enlisting the aid of special methods of investigation in suspect cases. The nature of the community greatly affects the accuracy of diagnosis, this is highest in urban communities with experienced specialists and ready means of transport, lowest in remote rural areas with few and scattered practitioners and poor transport facilities. "The motor car, by shortening the distances between patient and physician, unquestionably increases greatly the number of recognized cases of cancer" (Wells)

Grade 2

Grade 2 comprises clinical diagnoses made after supplementing simple physical examination by special physical or chemical methods of investigation—pathological radiological, endoscopic or operative, but without pathological study of excised tissues. In the hands of experienced specialists, these methods greatly enhance the accuracy of diagnosis of many internal tumours, especially those of the alimentary canal, urinary tract, lung and central nervous system. However, in the absence of pathological examination of excised tumours or of biopsy fragments, an important degree of diagnostic error still obtains with some of these classes of tumours. Many hospital cases fall into this grade of diagnostic accuracy.

Grade 3

Grade 3 comprises diagnoses made after histological examination of excised tumours or pieces of tumours. Histopathological diagnosis of surgical material is sometimes final and complete as for example from examination of an excised cancerous breast or stomach or kidney, or even of small biopsy fragments of such tumours or it may still be incomplete, as when examination of an enlarged lymph gland or of pieces of tissue from a tumour in the brain or in a bone or in the peritoneal cavity proves the presence of metastatic carcinoma or of some other neoplasm but still leaves its primary origin undetermined. Further not all histopathologists are of equal ability and experience, questionable diagnoses and archaic terminology are far from rare.

Grade 4

Grade 4 comprises necropsy diagnoses. Here also, the reliability of such diagnoses depends on the competence and experience of the investigator. Unreliable post mortem work is all too common and incomplete necropsies can, and frequently do, lead to erroneous diagnoses. Even competent pathologists can make occasional mistakes in diagnosis through incomplete examinations especially failure to preserve sufficient or appropriate material for subsequent histological study. I strongly maintain that any post mortem examination, unconfirmed histologically, is incomplete, not infrequently, microscopic examination surprises the clinician and pathologist by showing the falsity of the initial post mortem diagnosis even in cases where this appeared certain. Admittedly, diagnostic errors of this kind are not frequent with such familiar tumours as carcinomas of the breast, of the stomach of the intestines or of the uterus. Yet, even with these, errors *do* occur e.g. my own necropsy records contain instances of the following corrections of post mortem diagnosis necessitated by microscopic

examination—gastric carcinoma to 'chronic ulcer', and *vice versa*, 'carcinoma of the colon' to diverticulitis, and *vice versa* carcinoma' to 'sarcoma' of the stomach intestine breast and uterus. For many years, I have made it my practice to confirm microscopically all tumour diagnoses made *post mortem*. Clearly, for correct identification of tumours of the less frequent and familiar kinds competent microscopic study is essential. Experienced pathologists are, of course, aware of all of the foregoing considerations and the number of mistaken *post mortem* diagnoses which they will make should be statistically negligible.

Many large collections of tumour cases dealt with statistically, most notably the registered deaths from cancer, are mixtures of all four grades of diagnostic precision, with the lower grades 1 and 2 predominating. How much reliance can be placed on such mortality figures? Several writers conveniently summarized by Wells, have attempted to assess the degree of error in clinical cancer diagnosis as disclosed by necropsies in large series of hospital cases. These revealed diagnostic errors in from 27 to 43 per cent of cases—errors not merely of detail but concerning the presence or absence of malignant disease or its nature and primary site. Cleland's necropsy work (1942) disclosed—cancer correctly diagnosed 156 cases, site incorrectly diagnosed 10 cases, cancer present but undiagnosed, 27 cases, cancer diagnosed but not present 22 cases.

I have carried out a similar, carefully planned study of 1 000 relevant hospital necropsies to ascertain the extent of diagnostic error in cancer diagnosis as a whole and in the individual main groups of tumours. Although the series is small, I can at least claim scrupulous care in the collection of the data and the highest possible accuracy in the necropsy diagnoses all of which were verified or corrected by adequate microscopic examination. As will appear this study provides indications not only of the degree of error to be expected in mortality and other statistics but also of some important statistical pitfalls.

THE ERRORS OF CANCER DIAGNOSIS REVEALED BY 1 000 RELEVANT NECROPSIES

The investigation which was carried out at the Alfred Hospital Melbourne during the period July 1936 to December 1944 covered 1 000 consecutive necropsies in which either a clinical diagnosis of malignant disease had been made or malignant disease was discovered *post mortem*. The necropsies were performed by me personally or under my personal supervision and the final diagnosis of every tumour was established histologically. Those few cases in which specific diagnosis of the nature of the tumour still remained uncertain after necropsy study were excluded from the series. Little or no selection of cases for necropsy was exercised during the period investigated necropsies were done on 58 per cent of all fatal cases in the Hospital (namely 3 000 necropsies in 5 163 deaths excluding coroner's cases) and there were very few fatal cancer cases which escaped necropsy. (The law regarding necropsy in Victoria is noteworthy in this respect. Necropsy may be performed on any person dying in a public hospital unless an objection has been lodged. Very few objections are lodged so that necropsies are obtainable on nearly all cases. An enlightened law thus greatly favours pathological research as compared with that of countries in which

necropsy cannot be obtained without the specific permission of the next-of kin)

Whenever possible the clinical diagnosis of each case was discussed with the resident doctor concerned *before* the necropsy was performed, and the diagnosis which would have been recorded on the death certificate in the absence of a necropsy was ascertained. During the greater part of the period concerned, it was the practice for the doctor to insert in the progress records of each patient a special note indicating the clinical diagnosis reached. In some cases in which this was not done and in which pre necropsy consultation was impracticable, the clinical diagnosis which would have been made was nevertheless clear from the progress notes and the records of special investigations.

The clinical and necropsy diagnoses of any particular kind of primary tumour X fell into the following 5 groups

A—clinical diagnosis of X , verified by necropsy

B—no malignant disease diagnosed clinically, X disclosed by necropsy

C—malignant disease diagnosed clinically, but primary site incorrect or unspecified, X disclosed by necropsy

D—erroneous clinical diagnosis of X , some other primary tumour being disclosed by necropsy

E—erroneous clinical diagnosis of X , no malignant tumour of any kind being found at necropsy

Thus the total number of *actual* cases of X is the sum of $A + B + C$ ($B + C$ giving the total number of failures to diagnose X when it was present). The total number of clinical diagnoses of X is the sum of $A + D + E$ ($D + E$ being false positive diagnoses). The false total $A + D + E$, which shows the total number of death certificates which would have borne the diagnosis X if no necropsies had been performed, can be compared with the actual number of cases of X , $A + B + C$. The main results of the investigation are set out in the accompanying Table I which will now be discussed.

(1) General comments on the table

(a) *The total diagnostic error*

The 1 000 necropsies comprised 943 actual cases of cancer and 57 cases which had been wrongly diagnosed clinically as cancer. Of the 943 actual cases 647 (69 per cent) had been diagnosed correctly, and 296 (31 per cent) had been misdiagnosed. (If any significance is to be attached to the total "amount of cancer" irrespective of site—which is very doubtful—then the total number of cases correctly diagnosed was 817 ($A + C$) which is 87 per cent of the true total while the total number of cases diagnosed clinically as "cancer", i.e. the total number of 'cancer' death certificates which would have been recorded had no necropsies been performed, was 874 ($A + C + E$) which represents 92 per cent of the real number of cancer deaths. The findings thus suggest that the total number of 'cancer' deaths recorded in mortality statistics may be only slightly less than the real total.)

(b) *The statistical significance of positive and negative false diagnosis*

For any given kind of tumour X failures to diagnose it when present ($B + C$) and false positive diagnoses of X will partly cancel each other and indeed may result in a mortality figure closely approximating to the real one i.e. $A + D + E$

may approximate to, or may equal, $A + B + C$. For example, in the Table close approximation obtains for carcinomas of the stomach, pancreas or oesophagus. It is of the utmost importance, however, to recognize that the series of clinical diagnoses $A + D + E$ even though its total may be nearly correct is a false basis for any further analyses of the properties of X , e.g. as regards age, sex, social or racial incidence, clinical course or response to therapy. For not only does the series fail to include some real cases of X ($B + C$) but, far

TABLE I

Clinical or post mortem diagnosis	No of proven cases	Correct clinical diagnosis		Incorrect clinical diagnosis				Ratio $D + E$ A (approx.)
		A		B	C	D	E	
		No	%	No	No	No	No	
Carcinoma of stomach -	155	109	70	18	28	21	19	1.3
Carcinoma of large intestine -	145	117	81	14	14	11	8	1.6
Gliomas of brain -	83	74	89	8	1	9	3	1.6
Carcinoma of lung -	71	43	61	13	15	4	5	1.5
Lymphoid tumours -	57	38	67	11	8	—	1	1.38
Carcinoma of breast -	55	50	91	3	2	1	—	1.50
Carcinoma of gall bladder and ducts -	46	10	22	6	30	3	1	1.2½
Carcinoma of lip, oral cavity, pharynx, larynx, salivary glands -	38	32	84	—	6	—	—	0
Carcinoma of bladder -	34	26	76	5	3	2	—	1.13
Carcinoma of pancreas -	33	11	33	8	14	21	4	2.1
Carcinoma of prostate -	31	25	81	5	1	3	4	1.3½
Carcinoma of uterus -	25	19	76	2	4	4	2	1.3
Carcinoma of oesophagus -	20	13	65	3	4	4	2	1.1½
Carcinoma of kidney -	17	8	47	4	5	1	2	1.3
Miscellaneous -	133	72	54	26	35	3	4	1.10
TOTAL -	943	647	69	126	170	87	55	1.4½

more important it wrongly includes a heterogeneous collection of cases of other diseases ($D + E$) differing from X in their properties. These errors of inclusion ($D + E$) are more serious statistically than the errors of omission ($B + C$) because they falsify the data in a positive way and to an unknown extent. Such positive falsification will be greatest in those groups of tumours in which the ratio $D + E/A$ (given in the final column of the Table) is large, e.g. in carcinoma of the pancreas, oesophagus or stomach. Thus in spite of nearly correct totals ($A + D + E$) for these three tumours the clinical records uncorrected by the necropsy diagnoses would have been highly erroneous bases for any further analyses of their respective properties. On the other hand there were very few false positive diagnoses of carcinomas of the oral and neighbouring tissues, carcinoma of the breast, the malignant tumours of lymphoid tissue and carcinoma of the bladder, so that in spite of failure to diagnose a proportion of actual cases in some of these groups analyses of the uncorrected clinical records of cases so diagnosed would have led to nearly correct results, since little positive

falsification was introduced. For the whole series, the ratio $D + E : A$ was $144 : 647$, approximately $1 : 4\frac{1}{2}$, i.e. for every $4\frac{1}{2}$ specifically correct diagnoses, there was one specifically incorrect.

The total D , 87, does not enter into the total of 943 actual cancer cases, since it represents false clinical diagnoses of cases already included in group C . Thus a case of carcinoma of the stomach wrongly diagnosed clinically as 'carcinoma of the pancreas' is placed in group C as an actual case of carcinoma of the stomach misdiagnosed, while the false diagnosis 'carcinoma of the pancreas', which of course does not represent another actual case of cancer, is recorded in group D . If the incorrect diagnoses arising out of group C had always specified the supposed primary site of the tumour, then the total for group D would have been equal to that of group C . Actually, however, total C exceeds total D by 83, because there were 83 cases in which the clinician had displayed commendable caution in such diagnoses as 'abdominal malignancy', 'malignancy of uncertain origin', 'disseminated carcinoma', 'intra thoracic tumour', etc. Had no necropsies been performed, these non committal diagnoses would have appeared on the death certificates, but they would not have introduced a positive source of error into subsequent statistical analyses of the properties of any given kind of tumour.

That this series shows such a high proportion of non committal diagnoses of malignant disease—83 out of 943 actual cases (9 per cent)—is significant. This was due partly at least, to the wholesome caution engendered in the clinicians by the very knowledge that their diagnostic errors in fatal cancer cases would be exposed by necropsy. Hence, instead of yielding to the natural inclination of all mankind "to give all things a name", they more often frankly admitted their uncertainties and the inconclusive nature of available evidence. Such proper and scientific caution certainly does not obtain in the recording of death certificates in general: general practitioners are often well content to enter their tentative diagnoses without indicating any element of uncertainty. Indeed, practitioners whose diagnostic errors are rarely or never exposed by necropsy (and these practitioners are by far the majority) are themselves unaware of the frequency and extent of these errors. Hence they commit themselves to positive false diagnoses much more often than the hospital clinician, whose whole training and close association with the pathologist necessarily inculcate greater scientific caution. Until it becomes a general practice for death certification to include a statement of the bases of diagnosis—according to the four grades of precision suggested above—and for published vital statistics regarding each kind of tumour to show the proportions of the diagnoses of each grade, we will be unable to assess the probable degree of positive error in these statistics. A main intention of the present analysis is to show how great these errors are likely to be.

(c) *The selected nature of the cases*

The general question of the selected nature of hospital cases is discussed below. Here we are concerned only with the evidence of such selection in the present series and some of the reasons for it. Selection is apparent from the relative frequencies of the various kinds of tumours in the series. While two notoriously common tumours—gastric and intestinal carcinomas—head the list, two other common ones—mammary and uterine carcinomas—are lower than we

might have expected. The reasons for this are related largely to the differences in duration and therapy of the respective diseases. The radical surgery of gastrointestinal carcinoma had a relatively high immediate post operative mortality, and many other inoperable cases were admitted to hospital as surgical or medical emergencies (intestinal obstruction, severe haemorrhage, progressive anaemia, etc.) and proved rapidly fatal. On the other hand, the immediate post operative or post-radiational mortality of mammary or uterine cancer was small, and many of the recurrent cases were transferred to the Austin Hospital for Chronic Diseases for treatment in the later stages. Thus many deaths from uterine and mammary carcinoma, initially treated at the Alfred Hospital, did not take place in that Hospital. The fictitiously low figures for these two tumours in this series was *not* due to inequality in the numbers of males and females admitted to hospital during the period reviewed; the Alfred Hospital contained approximately equal numbers of male and female beds.

The high place occupied by glioma of the brain, third on the list, was due to the Alfred Hospital having had during the period reviewed the most active neurosurgical clinic in Victoria—indeed in Australia—and to its chief, Mr H. C. Trumble, having taken unusually keen interest in the pathological as well as the clinical aspects of his cases.

The series thus shows clearly, what Wells also has emphasized, that the relative frequencies of various tumours in the clinical and necropsy records of a general hospital are not the true relative frequencies, but are influenced by many extraneous factors. These include differences in rate of progress and in prevailing methods of therapy for different kinds of tumours; the proximity of a special cancer hospital or of other special hospital; and the presence in the general hospital (or, conversely, in neighbouring general hospitals) of special clinics or of enthusiastic individual specialists. Many other selecting factors are noted where this subject is discussed again more generally below.

(2) Comments on particular tumours in the table

(a) *Carcinoma of the stomach*

Of 155 actual cases of this disease, the clinicians had successfully diagnosed 70 per cent and had failed to diagnose 30 per cent. The ratio of positive misdiagnoses to correct diagnoses of carcinoma of the stomach ($D + E/A$) was high—more than 1.3. A series of cases showing such high proportions both of failures to diagnose and of erroneous inclusion of other diseases would clearly be valueless for any detailed analysis. Yet the total number of death certificates which would have been marked 'carcinoma of the stomach' if no necropsies had been performed ($A + D + F$) closely approximates to the true number—149 instead of 155. The tumours responsible for most of the 21 false positive diagnoses of group D were carcinomas of the pancreas, biliary tract or oesophagus. Of the 19 non-malignant cases which had been wrongly diagnosed as carcinoma of the stomach, 10 were cases of chronic peptic ulcer.

(b) *Carcinoma of the large intestine*

This has caused decidedly fewer diagnostic errors than carcinoma of the stomach. Correct clinical diagnosis was attained in 81 per cent of cases, and the ratio of false positive to correct diagnoses was less than 1 to 6. Of the 19

false positive diagnoses 11 were cases of neoplastic disease, in 6 cases carcinoma of the stomach

(c) *Carcinoma of the biliary tract*

A correct diagnosis was made in less than one quarter of the cases. Of the 36 failures to diagnose this disease, in 18 the erroneous diagnosis had been "carcinoma of the pancreas". Non necropsy records of biliary carcinoma are clearly valueless statistically.

(d) *Carcinoma of the pancreas*

Only one third of actual cases had been correctly diagnosed, and for every correct diagnosis there were 2 false positive diagnoses. Of the 25 false positive diagnoses 18 were cases of carcinoma of the bile ducts or gall bladder. If no necropsies had been done the number of deaths certified as due to "carcinoma of the pancreas" ($A + D + E$) would have been close to the actual number—36 instead of 33—but two thirds of the cases so certified would *not* have been cases of pancreatic carcinoma. Clearly, records of this disease, unconfirmed by necropsy, are statistically useless.

(e) *Carcinomas of the crano cervical passages*

These had been correctly diagnosed in 84 per cent of cases and there were no false positive diagnoses. Two of the 6 failures to diagnose were due to large metastases in the cervical lymph glands from small symptomless primary growths in the tonsil and pharynx respectively.

(f) *Carcinoma of the oesophagus*

Two thirds of actual cases had been diagnosed correctly, the ratio of false positive to true diagnoses was 1 to $1\frac{1}{2}$. Four of the 8 false positives were cases of carcinoma of the stomach.

(g) *Carcinoma of the lung*

Carcinoma of the lung had been correctly diagnosed in only 61 per cent of cases and the proportion of false positive to correct diagnoses ($D + E$) was 1 to 5. If no necropsies had been performed, the number of death certificates which would have borne the diagnosis 'carcinoma of the lung' would have been not more than 52 ($A + D + E$), i.e. 73 per cent of the actual number. Indeed the number would have been fewer than this because in several cases the clinician, relying mainly on radiographic reports, would have committed himself to no more specific diagnosis than 'pulmonary neoplasm' or even only 'intra thoracic neoplasm'. All of the 15 misdiagnoses of group C had been due to clinically obtrusive secondary growths. These were in the brain in 4 cases and the clinical diagnoses had been 'cerebral tumour' in a fifth case (of group B) cerebral metastases had led to a clinical diagnosis of "confusional psychosis".*

* Study of an enlarged series of 84 consecutive necropsies on cases of pulmonary carcinoma—the above 71 cases and 13 additional ones—gave the following results. Correct clinical diagnoses were recorded in 49 i.e. 58 per cent. Tumour was diagnosed but the primary site was wrongly diagnosed or uncertain in 19 cases. In 17 of these the main symptoms had been produced by secondary growths which were in the brain in 5 cases. Diagnoses of non neoplastic disease had been made in 16 cases—most of these had been diagnosed as pulmonary infections—tuberculosis, "abscess", pneumonia, bronchiectasis—but in 2 cases cerebral metastases had led to diagnoses of "psychosis" and "cerebral abscess" respectively. Thus metastatic growths in the brain had masqueraded as primary cerebral disease in 7 cases i.e. in 8 per cent of the series.

(h) *Carcinoma of the breast*

Carcinoma of the breast had been diagnosed correctly in 91 per cent of the 55 cases, and there was only one case of false positive diagnosis. This series thus confirms the general opinion that clinical diagnoses are of such a degree of reliability that they afford a valid basis for most statistical analyses of the properties of this disease.

(i) *Carcinoma of the uterus*

This had been correctly diagnosed in three quarters of the cases. False positive diagnoses had been made in the proportion of 1 to 3. However, selecting factors already referred to prevented this group from being a true sample of the disease, and gave a fictitiously high proportion of misdiagnoses. Many recurrent cases, nearly all of proven nature, were transferred in their later stages to the Austin Hospital for Chronic Diseases, while those dying in the Alfred Hospital included a disproportionate number of clinically unproven or unrecognized cases, and also of cases dying of post-operative complications.

(j) *Carcinoma of the bladder*

Carcinoma of the bladder had been correctly diagnosed in three quarters of the cases, and false positive diagnoses were infrequent.

(k) *Carcinoma of the prostate*

Carcinoma of the prostate had been correctly diagnosed in four fifths of the cases, but the proportion of false positive to true diagnoses was high—1 to 3½.

(l) *Carcinoma of the kidney*

This had been diagnosed correctly in less than one half of the cases, and the proportion of false positive diagnoses was 1 in 3.

(m) *Gliomas of the brain*

Gliomas of the brain were correctly diagnosed *ante mortem* in 89 per cent of cases. This relatively high degree of accuracy was due to the Hospital possessing, as already mentioned, a highly efficient neurosurgical clinic, and to the surgeon's usual practice of obtaining biopsy pieces for histological diagnosis of all brain tumours subjected to operation. On the other hand, the proportion of false positive diagnoses of 'brain tumour' (D + E A) was 1 in 6. Of the 12 false positive diagnoses, 8 were due to metastatic growths in the brain from unsuspected primary growths elsewhere, 4 of which were carcinomas of the lung, and the others included carcinoma of the thyroid, carcinoma of the kidney, and cutaneous melanoma.

(n) *Lymphoid tumours*

Lymphoid tumours—comprising lymphatic leukaemia, lymphosarcoma, Hodgkin's disease, and reticulosarcoma—had been diagnosed correctly in two thirds of the cases, and the number of false positive diagnoses was negligible. (The same applied to *myeloid leukaemia*, of which there were 10 actual cases, all correctly diagnosed, and one false diagnosis of 'leukaemia' in a case of unsuspected gastric carcinoma with a leukemoid reaction to metastatic deposits in bone marrow.)

(3) Conclusions on the series

About one third of 943 actual cancer cases had been misdiagnosed clinically. In many of the particular groups of tumours the ratio of false positive to correct diagnoses was so great as to invalidate any statistical analyses which might have been attempted of the clinical records uncorrected by the necropsy findings. This applied to carcinomas of the oesophagus stomach biliary tract pancreas lung prostate and kidney. Failures to diagnose a particular tumour—for most purposes statistically less serious than false positive diagnoses of that tumour—were so frequent in some groups as to render the clinical records (even including false positive diagnoses) of little value as an indication of the frequency of occurrence of the tumours in question. This applied particularly to carcinomas of the lung biliary tract and kidney. The tumours subject to fewest diagnostic errors were carcinomas of the breast cranio-cervical region and intestines and gliomas of the brain but in the last named group, the high degree of diagnostic accuracy was due to a purely local factor namely the presence in the Hospital of a busy efficient neurosurgical unit. The diagnostic difficulties and errors frequently recorded in the histories of many of the cerebral tumour patients showed that outside such highly specialized clinics the diagnosis of this disease must be highly erroneous. The series of cases of uterine carcinomas was too small and too selected to permit conclusions to be drawn but when allowance was made for the selecting factors it appeared probable that the diagnosis of this disease was fairly reliable.

In what follows I shall try to show to what extent these conclusions are applicable to various kinds of statistical figures and problems.

THE SELECTED NATURE OF HOSPITAL SAMPLES

As Wells pointed out hospital statistics are bound to be entirely misleading as to the frequency of cancer in different organs. This is because hospital cases are subject to varying degrees of selection in many ways both recognized and unsuspected. Some of the obvious selecting factors are the following—(1) the relative numbers of male and female beds and of adult and children's beds in the particular hospital, (2) the presence in the hospital of special clinics or wards for or of individual clinicians particularly interested in, special classes of cases e.g. gynaecological neurological radiotherapeutic, etc. or, conversely the presence of such special clinics or clinicians in neighbouring institutions, (3) the availability or otherwise of convalescent hospitals or after care homes to which the general hospital passes its more chronic cases, (4) the near presence of a special cancer hospital or radiotherapeutic centre which will divert from the general hospital many cancer cases often of highly selected kinds, (5) the situation of the hospital determining whether it serves communities predominantly urban or rural industrial or residential and whether or not it receives a disproportionate number of patients employed in particular local industries such as chemical or mining. These and other factors for which it is quite impracticable to make any quantitative allowances render hospital and other purely local statistics valueless as a basis for estimation of the relative frequencies of various tumours.

However, in a large city hospital with approximately equal numbers of beds for adult males and females these factors will usually play little part in selecting

cases *within* most of the specific groups of common tumours. Thus 100 cases each of say, carcinoma of the stomach, carcinoma of the lung and glioma of the brain admitted to a general hospital even into special clinics, are likely to constitute nearly average samples of those diseases as they occur in the community generally and therefore to be valid material for analysis of the properties of those particular tumours. That they may not be absolutely representative samples however, is noted by Hill, patients admitted to hospital are on the average more seriously ill than those not admitted, so that our 100 cases of gastric carcinoma will be sicker and therefore less favourable for treatment than 100 non-admitted cases of the same disease.

Post mortem cases may suffer selection in two special ways. (a) In communities in which the law requires that special permission for necropsy shall be obtained in each case or in which necropsies are relatively infrequent for any other reason clearly there must be much selection of cases. In such communities in relatively few hospitals are more than 20 per cent of the deaths followed by post mortem examination and the cases that are so examined are preponderantly the cases that offered difficulty in diagnosis during life (Wells). Of course under these circumstances no accurate estimates of the frequency of diagnostic errors are possible (As I have already been careful to point out this defect did *not* apply to my own series already analysed in which necropsies were done on 58 per cent of all fatal cases and very few fatal cancer cases escaped necropsy). (b) A less obvious but sometimes important kind of selection of necropsy cases depends on differences of duration, modes of therapy and surgical risks in different classes of tumours. We had instances of this in mammary and uterine carcinoma in the above series: the transfer of many recurrent cases of both diseases in their later stages to a special chronic hospital not only diminished the number coming to necropsy at the Alfred Hospital but in the case of uterine carcinoma led to some differentiation of cases according to the therapeutic results. Many groups of tumours are liable to such differentiation as regards cases coming to necropsy. Necropsies are likely to be obtained on cases dying in large general hospitals with adequate pathological departments i.e. on cases which succumb during radical surgical or other therapeutic procedures or those which have been retained in hospital because of metastatic or other special complications or because of diagnostic difficulties. Necropsies are less likely to be obtained on cases of non-complicated recurrent disease of proven nature and of long duration many of which in their later stages are transferred from the general hospital to other institutions or are returned to their homes. Such differentiation of necropsy cases will obtain most for diseases like uterine, mammary and skin cancer in which diagnosis is usually straightforward and in which vigorous potentially curative surgical or radiational treatment is often undertaken in the early stages. It will obtain least for many kinds of internal cancer such as gastric, biliary, pancreatic or pulmonary carcinomas which cause greater diagnostic difficulties, are often speedily fatal, and are often not amenable to surgical or radiational attack. Hence a consecutive unselected series of general necropsies on cases of any of these usually hopeless visceral tumours is likely to be a fair average sample.

The infrequency of post mortem examination in modern civilized communities is lamentable. It is self-evident that for statistical and research purposes far greater numbers of necropsies should be performed. At present in most English

speaking communities less than 5 per cent of deaths are followed by necropsies, with the remaining 95 per cent vast amounts of valuable pathological material, as well as many unsuspected misdiagnoses from which the medical practitioner regrettably learns nothing, are buried or burnt. No greater service could be done for both the progress of pathological knowledge and the elevation of the standard of medical practice than the enactment of legislation permitting—or better requiring—the medical practitioner to obtain a competent necropsy (at the State expense) in every case of uncertain diagnosis, before signing the death certificate. Were this to become a general practice, the sentimental antipathy of the public to necropsy (*not* really very strong even now) would soon disappear, intelligent doctors would welcome the opportunity of solving their diagnostic perplexities, observing the results of their treatment and learning from their mistakes, pathological science would receive a great impetus, and soundly based mortality statistics would become possible. 'We cannot have really reliable records until they are furnished by a large community in which for a period of several years all deaths are followed by post mortem examinations, and as yet there is not a community that has reached anything like this degree of enlightenment' (Wells)

HOW RELIABLE ARE CANCER MORTALITY STATISTICS ?

Mortality figures are based on the diagnoses (and misdiagnoses) written on death certificates. These diagnoses vary widely in their reliability—from those made from microscopically verified necropsies to mere guesses made under the worst conditions of remote or busy general practices. Diagnoses of the lower grades of reliability certainly outnumber those of the higher. Hence, as already insisted on until death certificates are made to specify the basis of diagnosis, thereby permitting them to be classified into grades of reliability, the amount of error in mortality figures must remain unknown. Under present methods of death registration, we do not know and cannot find out how great the error in the vital statistics may be. We are sure that there is some error, it probably is large but no one knows how large it is. A pathologist who does necropsies in many cases that have not been under the best hospital observation is likely to believe that the error is very large, and that conclusions of real value cannot be reached from the study of general mortality records. (Wells)

My studies outlined above not only endorse this opinion but permit particular conclusions regarding some of the main classes of tumours. These show that no reliance can be placed on the mortality figures for carcinomas of the stomach, oesophagus, pancreas, biliary tract and lung, and that those for carcinomas of the kidney and of the prostate are of doubtful value. The mortality figures for carcinoma of the breast and of the facio-cervical cavities are reliable, those for carcinomas of the intestine, of the uterus and of the bladder, and for the tumours of lymphoid tissue are less accurate but are probably useful for most statistical purposes. The general mortality figures for cerebral tumours are almost certainly highly erroneous. These conclusions applicable to countries with the least fallacious mortality statistics such as Great Britain, Australia, U.S.A. and the countries of pre-war Western Europe are still more cogent for many other countries with lower general standards of medical and pathological practice.

such as those of the U S S R the Balkans, South and Central America. In these the mortality figures for all but the most obvious of external tumours, such as mammary and oral carcinomas, must be entirely unreliable. For most Asiatic countries, of course no general mortality statistics exist.

THE AGE STATISTICS OF TUMOURS

(1) Age distribution and age incidence

In any analysis of the age relationship of a series of cases of tumour, or of any other disease the *age distribution* and the *age incidence* of the disease must be clearly distinguished. *Age distribution* states simply the numbers of cases falling in successive age periods in the series. Thus the age distribution of 1 060 proven necropsy cases of carcinoma of all kinds which I have personally examined was as shown in the horizontal column A of the following table.

TABLE II

	Decades - - - - -	1	2	3	4	5	6	7	8	9
A	No. of cases in each decade -	0	1	12	32	130	253	345	239	48
B	Percentage of cases in each decade - - - - -	0	0	1	3	12	24	33	22.5	4.5
C	Percentage of total population in each decade (approx) -	14	16	16	16	13	11	9	4	1
D	Ratios B : C - - - - -	0	0	0.06	0.18	1.0	2.2	3.7	5.6	4.5

The age distribution shown in columns A and B can be expressed graphically as in Fig. 1 (A). If a sufficiently large series of cases were available and were graphed to show the numbers in each year of age a continuous smooth curve as in Fig. 1 (B) would be obtained.

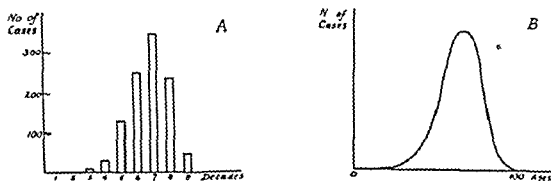


FIG. 1—(A) shows age distribution of carcinoma necropsies of Table II. (B) shows the smooth ideal curve of the age distribution of a large series.

Such a graph of age distribution however takes no account of the age distribution of the whole population from which the carcinoma cases came. In order to discover the relative liabilities of people of different ages to carcinoma we

INDEX

- Embryological classification of tumours 14-15
- Embryoma 976
- Embryonic tumours 7 15, 169, 740-743 747-752 756-758, 806, 815-819 843-869 879-896 925-937
- Enamel organ 308-310
- Encapsulation of tumours 21 22
- Encephaloid cancer 238
- Enchondroma 670-671 674-676 710
- Enchondrosis 670-671
- Enclavoma 321
- Endogenous carcinogens, 51 55 61 232, 435 439-440 597 937, 970
- Endometriosis 535
- Endometritis 534
- Endothelioma 11 184-185 304 321 359, 462 530 643, 645-647 686-687 693 696 702 718, 761 778
- Endothelium meaning of 11 645-646
- Enzymes in tumours 137 143
- Eosinophil leucocytes and eosinophilia with tumours 139, 530 771-777 795
- Ependymal spongioblastoma 803 804, 805
- Ependymblastoma, 802 803 814
- Ependymoma 185 803, 806 814-815 818
- Ephebo-genesis 976
- Epidermis (see *Skin*)
- Epididymis carcinoma of 579-580
 - cysts of 580
 - experimental tumour of 39
 - lymphangioma of 579 711
 - rhabdomyosarcoma of 751
 - secondary tumours of 465
 - teratoma of 573 943 948
- Epignathus 952-953
- Epiphyses tumours of 678 682
- Epithelial cavities, invaded by tumours 162-163 531
 - metastasis by implantation in 186-189
- Epithelioma 269
- Epithelium meaning of 11
- Eponyms inappropriate 774-775
- Epulis 685-686 745
- Ergot, 841
- Erythraemia 797-799
- Erythroblastoma 797-799
- Erythroblastosis foetalis 794
- Erythrocythaemia 797-799
- Erythroleukaemia 795
- Erythroplasia 287 290 597
- Ethyl-cholanthrene 33
- Eustachian tube carcinoma of 300
 - invaded by tumours 162
 - rhabdomyosarcoma of 741
- Ewing's tumour of bone 686-687 858 865-868
- Exostoses 120 671-674 919
- Expansive growth of tumours 21 22 147, 206
- Experience important in histopathology 21
- Experimental carcinogenesis 29-65 203 (see also under particular regions, types of tumours, animals and carcinogenic agents)
 - cumulative effects in 42
 - induction period of 30 33-36 42
 - precancerous changes in 40-42

INDEX

- Dermatofibroma 650
- Dermoid cysts 944 (see also *Teratomata*)
- Desmoid tumour 650-651
- Desmoplasia 136
- Desoxycholic acid 32 33 34 61 435
- Diabetes associated with cancer 197 448
- Diagnosis chemical tests in 145
 - difficulties and errors of 67-76 171-172 184-185 204 243 244 245 298 301 304 359-360 371-376 408-410 437 440-441 443 447-449 462-465 482-483 587 590-591 610-612 617 627 669-670 702-703 761 776 784-786 840 844 864-868 907-909 912 915
 - improvements in 85 360 391-392
- Diamino-dinaphthyl 44 46
- Diaphyseal aclasis 671-672
- Dibenzacridine 32 34 35
- Dibenzanthracene 3 32-44 48
- Dibenzcarbazole 32 34 39 44 46
- Dibenzfluorene 32 34
- Dibenzpyrene 34
- Diktyoma 895-896
- Dimethylaminoazobenzene 44-46
- Dimethyl benzanthrane 32 33 35 36
- Distosomiasis 434
- Dog experimental tumours in 30 31 46
 - Hodgkin's disease in 780
 - spontaneous tumours in 94-95 117 119 140 211-213 221 226 263 264-265 306 323 361-362 393 420-421 432-433 439 445 457 470 510-512 524 548 552 555 562-564 579 580 586 597 604 612-613 630 634 639 654-655 666 689-690 713 780-781 796 799-800 820 841 874
- Dopa test 904 911
- Duck transfer of fowl tumour to 100
- Duodenum adenoma of 413
 - carcinoma of 412 413
 - invaded by gastric carcinoma 157 404 406
 - leiomyoma of 734
 - polyp of 412-413
 - secondary tumours of 991
 - ulcer associated with carcinoma of 413
- Dural sinuses invaded by tumours 683 721 726-727
- Dura mater chloroma of 797
 - endothelioma of 718
 - secondary tumours of 178 242 245 431 797-799
- Duration of tumours 82-83
- Dusts possibly carcinogenic 54 363
- Dyschondroplasia 671
- Dystrophia adiposogenitalis 628 630 658
- Ear carcinoma of 30 47 55 56 109
 - neurilemmoma of 841
 - secondary tumours of 464 683
- Ecchondroma 675-677
- Ecchondrosis 918
- Ecchordosis 918-919
- Ehrlich mouse carcinoma 100
- Emboli and embolism from tumours
 - abortive 175 178-180 206
 - in blood vessels 172-177 430 436 672 732 749
 - in lymph vessels 166-171

Kidney (*cont*)

carcinoma of (*cont*)

prognosis of 459 463

race incidence of 457

sex incidence of 81 457

site of 457

structure of 458-462

• veins invaded by 158 159, 459

carcino sarcoma of 461

embryonic tumours of 96 97 101 120, 925 932

in myelomatosis 788

leiomyoma of 453 736

lipoma of 453

lymphangioma of 711

mixed tumours of, 461 756 925-932

nephroblastoma of 925-932

osteosarcoma of 689

rhabdomyosarcoma of 756

sarcoma of 461 689

sclerosis of preceding tumours 454 457

secondary tumours of 178 242, 303 410 426 430 431 463 477 770 797-799 919 991

teratoma of 931

tumour-emboli in 176

Kidney pelvis, Brunn's nests in 471-472

calculi in 472 640

carcinoma of 38 46 81 168 188 189 467-477

implantation of tumours in 189

leucoplakia of 468 471-472

metaplasia of 471-472

papilloma of 467-477

pyelitis of 471-472

secondary tumours of 189

Kraurosis 287 290, 549

Krukenberg's tumour 405 408-409 425 492

Kultschitzky cells 414-415

Lachrymal glands and ducts tumours of 286

Lactic acid anti-carcinogenic 31

in tumours 26 144 150

Langerhan's islands tumours of 450-451

Lanolin anti-carcinogenic 31

Large intestine adenoma of 421-423

carcinoma of 419-428

age incidence of 81, 419

anal 427-428

appendical 426-427

argentaffin 424

causation 421-424

diagnostic errors in 71 73 423, 425

frequency of 419

gastric polypi accompanying 396

heredity and 421-422

in animals 420

inflammations preceding 423-424

metaplasia in stroma of 139 424

metastases of 168 421 425-426

mode of origin of 115-116

multiple 420-423

INDEX

- Experimental carcinogenesis (*cont*)
 - site affecting 31
- Eye (see also *Retina Choroid Conjunctiva*)
 - melanoma of 911-913
 - melanosis of 914
 - secondary tumours of 375 464
- Eyelids
 - adenoma in dog 95
 - carcinoma of 95 265-267
 - tumours of tarsal glands of 286-287
- Facial cleft carcinoid 273
- Faeces carcinogens in 424
- Fallopian tube carcinoma of 516-521
 - chorion epithelioma of, 985
 - implantation of tumours in 188 539
 - papilloma of 520
 - pregnancy of 985-986
 - salpingitis 518-520
 - secondary tumours of 188 516-517 531 532 539
 - spread of tumours through 531 539
 - teratoma of 945
 - tuberculosis of 516 519-520
 - Walthard rests of 490
- Familial tumours (see *Heredity*)
- Fibro-adenoma 211-220
- Fibro lipoma 661-663
- Fibroma 647-655
 - in animals 95-99 654-655
 - of abdominal wall 649 650-651
 - of bone 651-652
 - of meninges 725
 - of nasal cavity 651-652
 - of nerves 649 655
 - of ovary 484 496 653
 - structure of 647-648
- Fibro-papilloma 211
- Fibrosarcoma 647-655
 - experimental 35-36 39 58
 - in animals 94-97 654-655
 - metastases of 168 649 655
 - of bone 648-649 651
 - of heart 654
 - of lung 135
 - of lymph glands, 774 777-780
 - of muscle 649
 - of nerves 649 655
- Field fire carcinoma 275
- Fields of origin of tumours 106-125 204-205
- Filterability of tumours 58-60 100-101 195
- Fingers carcinoma of 263
- Fish tumours in 98 604 654 689 756 841 869 915
- Flexner Jobling rat carcinoma 99
- Fluorescence spectra 31 33 34
- Foetus affected by maternal tumours 906
- Foetus in foetu 976
- Fordyce's disease 276-277
- Fowl experimental tumours in 30 35 47 58-60
 - spontaneous tumours in 58-60 97 100 101 139 306 361 387 393 433, 439 510 634

INDEX

- Liver adenoma of 434
- angioma of 96 708 709 713
- carcinoma of 430-437
 - age incidence of 430-432
 - arising in cysts 117 435
 - bile secreted by 130 436
 - causation of 433-435
 - cirrhosis and 124 430-431 433-434
 - diagnostic difficulties with 431 437
 - experimental 39 40-47
 - frequency of 431
 - haemochromatosis and 118 124 434 435
 - in animals 94 95 96 98 432-433
 - metastases of 168 178 183 430-431 436-437
 - mode of origin of 118 436
 - multicentric 436
 - parasites and 434
 - race incidence of 431 432 434
 - sex incidence of 430-432
 - structure of 430-431 436
 - thoracic duct invaded by 431
 - veins invaded by 430 431 435 436
- cholangioma of 436
- cirrhosis of 124 430-431 433-434
- cystic disease cancerous 117 435
- cysticercus tumours of 58 97
- embryonic tumours of 932-935
- extracts of carcinogenic 61
- haemochromatosis of 118 124 434 435
- hepatic veins invaded by tumours 158 430 431 436
- hepatoblastoma of 932-935
- hepatoma of 436
- hyperplasia of 124
- inflammations of 434-435
- metastatic growths favoured in 179
- parasitic disease of 434
- portal embolism from tumours 175
- sarcoma of 58 99
- secondary tumours of 133-134 158 178 179 242 244 303 374 409 416 425 440 449 463 477 488 532 680 727 734-735 770 797-799 85\ 864 913 919 920 923 991
- selective carcinogens for 435
- Lizards tumours of 98
- Lucke's frog tumour 60 98
- Lungs and bronchi
 - adenoma of bronchus 376-382
 - adenoma of lung 361
 - adenomatosis of lung 384
 - angioma of 709 713
 - anthracosis of 363
 - asbestosis of 363
 - bronchitis bronchiectasis 58 361 362-363 365 371
 - capillaries traversed by tumour cells 177
 - carcinoma of 359-384
 - age incidence of 81 360-361
 - apical 366 372
 - arsenic and 365
 - causation 53-54 362-366
 - cells in pleural fluid 180 181

- Large intestine (*cont*)
 - carcinoma of (*cont*)
 - polypi accompanying 396 421-423
 - prognosis of 425
 - sex incidence of 81 419
 - site of 419-420
 - social class and 88
 - structure of 424
 - veins invaded by 172 424
 - diverticulosis and diverticulitis of 424
 - dysentery of 424
 - inflammatory diseases of 423-424
 - leiomyosarcoma of 734-735
 - papilloma of 421-423
 - polypi and polyposis 89 90 115-116 125 421-423
 - ulcerative colitis of 423-424
- Larynx
 - carcinoma of 81 88 188 302-303 306
 - chondroma of 675
 - papilloma of 302-303
 - plasmocytoma of 790
 - secondary tumours of 464
- Lead in tumour treatment 103
- Leiomyoma (see also under particular regions) 52 94-96 119 245 453 497 530 533 535-536 729-737
- Leiomyosarcoma 35 37 168 173 729-737
- Leontiasis ossea 673
- Lepidoma 14
- Leucocytes in tumours 138-139 150
- Leucocytosis with tumours 139
- Leucoplakia (see under particular regions)
- Leucosarcoma 761
- Leukaemia aleukaemic 761
 - associated with erythrocythaemia 795 797
 - associated with pernicious anaemia 795
 - basophil-cell 794 796
 - causation of 781 796
 - chloroma with 796-797
 - congenital 794
 - diagnostic errors in 75
 - eosinophil-cell 794
 - experimental 37 47 781
 - in animals 95 97 101 780-781 796
 - lymphocytic 761 764-771 782
 - mitosis in cells in 794-795
 - mode of origin of 119 792-794
 - monocytic 800
 - myelogenous 792-796
 - occupational 781 796
 - plasma-cell 788
- Leukanaemia 795
- Light as a carcinogenic agent 55 110 259-260 294
- Lindau's disease 710
- Lion tumours in 420 524
- Lip carcinoma of 89 114 293-295
 - salivary tumours of 324
- Lipoma 95 96 98 119 657-663 666
- Liposarcoma 35 58 129 663 666
- Lipomatoid lesions 657-658

INDEX

Lungs and bronchi (*cont.*)

- pulmonary embolism from tumours 172-175 430, 436 672 732 749
- rhabdomyosarcoma of 755 756
- secondary tumours of 149 154 163 178 187-188 242 244 303 343 405 407 409
426 430-431 436 441 447-449 463, 475 477 489 506 532 542 605 613 677
680 683 689-690 699, 727 731-733, 749, 770 775-776 848 857-858, 868 919
972 991
- siderosis of 363
- silicosis of 363
- squamous metaplasia of 58 126
- transplantation of tumours by intra bronchial route, 187-188 302, 315
- tuberculosis and tumours of 362

Lymph glands and lymphoid tissue

- barrier function of 169
 - carcinoma metastases in 166-172
 - diagnostic errors in tumours of 171-172 298 301, 304 374 390 391, 476 590 761
 - endothelioma of 172 761 778
 - fibrifying sarcoma of 774 777-780 782
 - follicular lymphoma of 761 763-764 782
 - histogenesis of 760-761
 - histogenetic kinship of tumours of 761-763 774 781-782
 - Hodgkin's disease of 762, 771-777 780 782
 - hyperplasia of 169 762
 - lymphoma of 763-764 782
 - lymphosarcoma of 135 761 764-771 780 782
 - melanoma metastases in 169 908
 - nomenclature of tumours of 17 760-762
 - primary and secondary tumours confused 171-172 298 331 304 374 390 391 476 590
761
 - primary tumours of 760-782
 - age incidence of 765 771
 - causation of 781
 - classification of 17 762-763
 - experimental 37
 - Gordon's test with, 777
 - histogenesis of 761-763 774 781-782
 - in animals 94-97 769-770 780-781
 - lymphocytic leukaemia with 761 764-771
 - metastasis of 168 769-771 775-777
 - mode of origin of 119 769-770 775
 - nomenclature of 17 760-762
 - sex incidence of 765 772
 - site of 765-767 772
 - structure of 764, 767-769 772-775
 - veins invaded by 769 775-776
 - reticulosarcoma of 761 777-780 782
 - syncytial sarcoma of 761 777
 - secondary tumours of 166-172 (and see under particular primary tumours)
 - stimulating primary tumours, 171-172 298 301 304 374 390-391 476 590 761
- Lymphadenoma 771
- Lymphangioma 710-713
- Lymphatic leukaemia 761 764-771
- Lymphatics metastasis via 166-172
 - retrograde embolism via 170-171
 - spread of tumours by 153-157 166-172, 405
- Lymphoblastoma 761 762, 764 768 771
- Lymphocytes in tumours, 138

INDEX

Lungs and bronchi (*cont*)

carcinoma of (*cont*)

- cells in sputum 373
- classification of 367
- complications of 372
- diagnostic errors in 71 74 185 359-360 371-376 617
- duration of 372-373
- experimental 37-38 46 53-54
- frequency of 359-360
- growth of 371-373
- heredity and 365
- histogenesis 367-371
- Hodgkin's disease simulating 775-776
- hydrocarbons in causation of 37-38 53-54 363-364
- in animals 37 95 97 361-362
- in Schneeberg and Joachimsthal 364
- increase of 359-360
- infections and 362-363
- metastases of 142 168 178 185 373-376
- minute 371-372
- mode of origin of 369
- oat-celled 369
- occupational 363-366
- pneumoconiosis and 363
- pneumonia and 363
- pulmonary artery invaded by 161
- racial incidence of 361
- radio-activity and 54 364
- sex incidence of 81 361
- siderosis and 363
- site of 366
- size of 371-372
- spread of 372
- squamous metaplasia in 126 367
- structure of 367-371
- trauma and 365
- tuberculosis and 362
- variation of structure in 128 129 367-369
- veins invaded by 372
- chondroma of 382-384
- fibro-adenoma of 382-384
- fibrosarcoma of 135
- hamartoma of 382-384
- Hodgkin's disease of 775-776
- implantation metastases in 187-188 302, 315
- infections of preceding tumours 362-363
- influenza preceding tumours of 362
- intra alveolar spread of tumours in 136 163 447 448 475
- invaded by rodent ulcer 275
- leukaemia of 793
- limphosarcoma of 766 767
- lymph vessel carcinosis of 144 409
- metastatic calcification of 640
- mixed tumours of 382 384
- neovascular of 447-448
- papilloma of 382
- pleurocytoma of 790
- pneumoconiosis of 363

INDEX

Melanoma (*cont.*)

- of mucous membranes 910
- of rectum 910
- of skin 899 909
- of vagina 910
- prognosis of 908 912
- rice ind 906
- simulated by carcinoma 129
- simulating Paget's disease of skin 288
- structure of 907-909 912

Meningitis of meninges eye and skin 913-915

Meninges (see also *Dura mater*)

- angioma of 710
- arachnoid fibroblastoma of 718-727
- diffuse tumours of 162-163, 720-721
- endothelioma of 718
- glioma of 808
- histogenesis of 718
- melanoma of 913-915
- melanosis of 913-914
- meningioma (see *Meningioma*)
- neuroglia heterotopic in 808
- osteoma of 725
- psammoma of 718 724-725
- sarcoma of 186 815
- secondary tumours of 185-186 375 410, 449-450 815-816 820 824-826 883-884 892
- tissue culture of 149

Meningioma 718-727

- age incidence of, 719
- angiomatoid 703 725
- associated with angioma, 720
- associated with neurofibromatosis 719-720, 835
- basal cranial 638 719
- brain invaded by 726
- causation of 720
- diffuse 720-721
- frequency of 718-719
- histogenesis of 718
- hyperostosis with 721-722
- invasive growth of 726-727
- metastasis of 727
- mode of origin of 119 721
- multiple 719
- ossified 725
- sarcomatous 726
- sex incidence of 719
- site of 719
- structure of 720 726
- tissue culture of 149
- venous sinuses invaded by 721 726-727
- ventricular 719-720

Meningiosarcoma 726

Merkel Ranvier cells 905

Mesenchyme and its tumours 17, 149 642-647 667-668 693 703 713, 752-755, 757

Mesenchymoma 643 713

Mesenteric tumours of 97 711 852 949

Mesencephroma 507-509

Mesothelioma 11 184-185 321 646 693 699

INDEX

- Lymphocytoma 761 764 768
- Lympho-epithelioma 297 299-301 305 355 621-622 766
- Lymphogranuloma 771
- Lymphoma, 763-764 782
- Lymphosarcoma 135 761 764-771 780 782
- Lymph stasis and cancer 194

- Macroglossia neurofibromatous 835
- Macrophages in tumours 139 448
- Madelung's disease 657
- Malformations distinguished from tumours 6-8 940-941
- Malignancy changes gradual 41-42
 - distinguished from benign 12-13 19-28 202-203 644
 - meaning of 12
- Mamma (see *Breast*)
- Mammals tumours in 94-97 (and see under particular species)
- Mandible (see *Jaws and Dental tissues*)
- Marjolin's ulcer 260
- Maxilla (see *Jaws and Dental tissues*)
- Maxillary sinus (see *Nasal cavity and sinuses*)
- Meckel's diverticulum tumours of 417 418 734
- Mediastinum Hodgkin's disease of 775-776
 - neurilemmoma of 828
 - neuroblastoma and ganglioneuroma (see *Neuroblastoma and Ganglioneuroma*)
 - sarcoma of 359-360
 - teratoma of 943 950-952
 - tumours misdiagnosed 359-360 372
- Medullary cancer 238
- Medulloblastoma 185 186 806 815-818 820 852
- Medullo-epithelioma 818-819
- Meibomian glands tumours of 281
- Meissner's corpuscles 833 905
- Melanin 899-916
- Melanoblastoma 899
- Melanoma 899-916
 - age incidence of 906
 - amelanotic 288 907-908
 - causation of 905-907 912
 - diagnostic errors in 907-909 912 915
 - epibulbar 910-911
 - experimental 31
 - frequency of 905 906
 - histogenesis of 904-905 911-912 915-916
 - in animals 94 95 96 98 915
 - injury and 906-907
 - lymphatic spread of 154 169, 908-909
 - maternal transferred to foetus 906
 - metastases of 169 178 908-909 912-913
 - mode of origin of 114 904
 - moles preceding 906
 - of adrenals 915
 - of brain 913-914
 - of cervix uteri 910
 - of conjunctiva 910
 - of eye 911-913
 - of gall bladder 915
 - of meninges 913-915
 - of mouth 910

must compare the percentages of the cases in the successive age periods with the percentages of the general population in those same age periods. Let us assume—as figures given by Crockett (1943) show, the assumption will be nearly correct—that in the population from which the foregoing carcinoma cases came the percentage of people in the successive decades were the same as those in England and Wales in 1938 which are given approximately in the horizontal column C. The column D gives the successive ratios B/C, which express the relative liabilities of people of different ages to develop carcinoma. It will be seen that the incidence of fatal carcinoma rises steeply and continuously into old age (the figures for the ninth decade are unreliable because the number of cases is too small).

As another example of the important distinction between age distribution and age incidence of tumours, Lane Claypon's figures regarding carcinoma of the breast may be cited. Analysis of 4,301 surgical cases (1924) showed the following percentages of cases in successive decades

TABLE III

Decade	—	—	—	—	—	3	4	5	6	7	8	9
Percentage of cases	—	—	—	—	—	1.8	15.5	35.5	28.2	15.1	3.3	0.6

But a curve of the mortality rates for mammary cancer per 1,000 of female population living in successive age periods (1928) shows a continuous rise from youth to old age. The same is shown in Table IV.

TABLE IV
AGE AND BREAST CANCER U.S. REGISTRATION STATES 1930
(From Bogen 1935)

Ages	Population	Deaths from breast cancer	Rates per 100 000	Percentages of total
0-14	34 180 745	5	0.01	0.05
15-24	21 235 387	21	0.10	0.20
25-34	18 017 199	290	1.61	2.68
35-44	16 451 562	1 441	8.76	13.32
45-54	12 487 707	2 671	21.42	24.68
55-64	8 086 614	2 935	36.30	27.10
65-74	4 559 756	2 107	46.20	19.44
Over 75	1 841 550	1 354	73.60	12.50
All ages	116 950 331	10 831	9.27	100

In mortality statistics, the age incidences of tumours are conveniently expressed, as in Table IV, in mortality rates per 100 000 of persons living in the respective age periods. But in non mortality statistics, ratios as in Table II must be used to assess relative liabilities to particular tumours at various ages.

(2) Modal and mean ages

The peak of the curve in Fig. 1 shows the *modal age* (i.e. the most frequent age) of death from carcinoma in the series considered. This is not the same as

INDEX

- Mesothelium meaning of 11
- Metabolism of tumours 143-145 150 179
- Metacarpals chondroma of 671 674-675
 chondrosarcoma of 676
 myeloma of 786
 secondary tumours of, 463
- Metallic impregnation stains 137-138 760-761 804-805 853 856 857 859 881
- Metaplasia bony in non neoplastic tissues 642 754 896
 bony in tumour stroma 101 139 218 336 381 424 550 589 621 629 729 749
 bony in tumour tissue 102 126 212-213 216 218 220 612-613 688 725
 cartilaginous in tumour stroma 101 139 218 336 538 561 612-613 749
 cartilaginous in tumour tissue 58 102 126 211-213 216 688
 epidermal in cervix and vagina 910
 mesenchymal tissues prone to 642-644 668 754 755
 mucoid in epithelial tumours 126 238-239 240 275 283
 muscle produced by 543-544 754-755
 squamous in epithelial tumours 126 127 239 241 329 330 352-353 355 367 404 424
 440 488 537-538 578 587 601 606
 squamous in non neoplastic epithelia 45 58 284 446 587-588
- Metastasis metastases 21 24 166-189 206 (see also under particular primary tumours)
 by blood stream 172-180
 by cerebrospinal fluid 185-186
 by coelomic spaces 180-185
 by implantation on epithelial surfaces 186-189
 by lymph stream 166-172
 delayed 244 407 462 680 912-913 972
 distribution determined by properties of tissues 178-180 206
 experimental study of 100-101 769-770
 in adrenals 178 242 297 303 342 368 374 410 426 449 463 477 677 991
 in bladder 303
 in bones 136-137 156 178 242 244 303 375 409-410 426 430-431 437 449 463
 477 532 540 590-594 611-612 677 680 697, 770 857-860 864-868 893
 912 932
 in brain 136 178 242 244-245 303 368 370 371 374-375 390 410 430 449 463-464
 477 680 776-777 908-909 991
 in breast 343 410
 in choroid 464
 in dura mater 178 242 245 797-799
 in ear 464
 in eye, 375 464
 in gall bladder 178 303 376 430
 in heart 178 242 303 342 376 410 461 463 477 677 770 909 919 991
 in hydrocele 185 375
 in intestine 178 242 245 303 375 430 770 785 908 991
 in iris 464
 in jaws 463
 in kidneys 178 242 303 374 410 426 463 477 770 797-799 919 991
 in larynx 464
 in liver 133-134 158 178 242 244 303 374 409 416 425 436 440 449 463 477 488
 532 680 727 734-735 770 797-799 855 864 913 919 920 923 991
 in lungs 148 163 178 242 244 303 343 405 409 426 436 440 447-449 463 477 489
 506 532 542 605 613 677 680 683 689-690 699 727 731-733 770 775 857-858
 868 919 972 991
 in lymph glands 166-172 242-243 271 303 373-374 425 610-611
 in meninges 185-186 375 410 627 820 824-826
 in metacarpals 463
 in mouth 142 375-376 464
 in muscles 178 303

INDEX

Metastasis metastases (*cont*)

- in ovaries 178 242 376 405 408-409 425 532 539 912, 991
- in pancreas 178 242 303 376 463 991
- in penis 465
- in pericardium 161 183 185 242 372 374
- in peritoneum 161 180 185, 242 374 408, 485-486, 972
- in phalanges 463
- in pituitary gland 376 991
- in placenta 410 909
- in pleura 161 180-185 242 374, 619-620
- in prostate 376
- in skin 178 240 241 375 410 449 460 464 506, 677 680, 770 912 919
- in spermatic cord 465
- in spleen 178 242 245 303 342 343 376 618, 797-799 865 919 991
- in stomach 178 303 430 785 991
- in testis 376 909
- in thyroid 159 178 242 245, 303 369 376 410 430 449 463 464 477 919 991
- in tongue 375
- in uterine myomas 245 731
- in uterus 242
- in vagina 176 465, 532 540, 990-991
- in vulva 176 465 540 990 991
- localization of 178-180
- manipulation affecting 100
- mitosis in 179
- superimposed cycles of 174
- surgical procedures affecting 100
- tissues as soils for 178-180
- transcoelomic 180 185
- vital staining affecting 101

Metatarsals myeloma of 786

Methyl-cholanthrene 32-44 55

Micro dissection of tumour cells 149

Middle-ear carcinoma of 300

rhabdomyosarcoma of 741

Mikulicz's syndrome 344

Milk factor in breast cancer 51-52 226

Milk stasis in breast cancer 50-51, 227-228 233-234

Mimicry in tumours 129-130 205

Mitosis in tumours 2 21 23 127 132-135, 179 181, 197 251-253 370 488 794-795 887

Mixed tumours 2 101 139 141

of breast 218 755

of kidney 461 756 925-932

of liver 756 932-935

of lung 382-384

of salivary glands 320-341

of thyroid 612-614 690

of uterus 542-544 752 755

transplantation of 101-102

Molluscs tumours of 99

Mongolian spot 910

Monilia in tumours 447-448

Monitor tumours of 98

Monkey (*see Primates*)

Monocytic leukaemia, 800

Motility of tumour cells 149

Mouse experimental tumours in 30-57, 492 510 527 587

spontaneous tumours in 97 99 100 101, 226 267 318 361 393 420 445 457, 524, 689

- Mouse (*cont.*)
 - spontaneous tumours in (*cont.*)
 - 769-770 780-781 796 820 826 973
- Mouth carcinoma of 71 74 81 82 87-89 94-98 293-304 (see also under particular regions)
 - leiomyoma of 733
 - melanoma of 910
 - plasmocytoma of 790
 - secondary tumours of 142 241 375-376 464
- Mucoid carcinoma 130, 238-240 329-333 351 353 367-370 388 403-405 424 440 447-448 474 487 541 587
- Mucoid metaplasia (see *Metaplasia*)
- Mule tumours in 387
- Mule spinner's cancer 29 258 259 598-599
- Multicentric origin of tumours 110-120 (and see under particular tumours)
- Muscle (voluntary) angioma of 705-706
 - fibrosarcoma of 649
 - heterotopic 757
 - in hepatoblastoma 756 933
 - in nephroblastoma 756 930-931
 - invaded by tumours 153
 - lipoma of 662-663
 - liposarcoma of 664
 - metaplastic formation of 754-755
 - osteogenic and cartilaginous tumours of 688
 - regeneration of 745-747
 - rhabdomyosarcoma of 740-743 756
 - secondary tumours of 178 179 303
- Mussel tumours of 99
- Mustard gas 43
- Myasthenia gravis 621-622
- Mycosis fungoides 762 770 782
- Myelogenous leukaemia 792-796
 - Myeloma (myeloid sarcoma myeloid tumour) 680 693 696
- Myelomatosis 784-789
 - Myoblastoma 742-747
- Myo-epithelium 283
- Myoma (see *Leiomyoma Rhabdomyoma*)
- Myxofibro-adenoma 216
- Myxoma and myxosarcoma 98 100 653-655 664-665
- Naevi acanthotic 268
 - blue 910
 - hairy 910
 - pigmented 899 904 914
 - sebaceous 281
 - vascular 700 715
- Naphthylamine 39 46 47
- Napoleon Bonaparte's necropsy 401
- Nasal cavity and sinuses
 - adamantinoma of 353-357
 - adenoma of 346
 - carcinoma of 96 126 349-358
 - chondrosarcoma of 658 690
 - epithelial tumours of 349 358
 - fibroma of 651 652 655
 - glioma of 808
 - inflammations of preceding tumours 357
 - lympho-epithelioma of 355

INDEX

- Nasal cavity and sinuses (*cont.*)
 - malignant granuloma of 652
 - melanoma of 910
 - myxoma of 651
 - papilloma of 351-353 355
 - plasmocytoma of 790
 - polypi of 651-652
 - rhinoscleroma preceding tumours 357
 - salivary tumours of 356-357
- Nasopharynx carcinoma of 299-302
- chondrosarcoma of 688
- juvenile fibroma of 652
- plasmocytoma of 790
- Native races tumours in 84 (and see under particular tumours)
- Necropsies importance of 68-72 77-78
- Neoplasm neoplasia (see *Tumour*)
- Nerve supply affecting tumour growth 142
- Nerves angioma of 705 708
 - fibroma and fibrosarcoma of 96 649 651 654-655 837-839
 - in teratomas 958 964
 - in tumours 141-142
 - invaded by tumours 154-156
 - myxoma of 654 838
 - neurilemmoma of 98 828-835 839-840 841
 - neuroblastoma and ganglioneuroma (see *Neuroblastoma and ganglioneuroma*)
 - neuro epithelial tumours of 840-841
 - neurofibromatosis of 120 660 719-720 832 835-841 872
 - perineural lymphatic permeation by tumours 154-156 590 594
 - rhabdomyosarcoma of 755 756
- Neural tissues tumours of 18 802-897
- Neurilemmoma 98 733-734 828-835 839-840 841
- Neurinoma 98 828
- Neuroblastoma and ganglioneuroma 843-869
 - age incidence of 848-851
 - calcification in 856
 - definition of 843
 - diagnostic errors with 844 864-868
 - Ewing's tumour and 687 858 865-868
 - histogenesis of 862-864
 - historical outline of 843 847
 - in animals 98 869
 - malformations with 854
 - maturation of 856 863
 - metastases of 848 855 857-861 864-869
 - multicentric origin of 120 852
 - nomenclature of 845-846
 - sex incidence of 851
 - sites of 851-854
 - structure of 854-864
- Neurocytoma 845 852
- Neuro-epithelioma 806 814 818-819 880
- Neurofibroma and neurofibromatosis 96 120 649 660 719-720 832 835-840 841 872
- Neurofibromatoid changes with pigmented moles 901-905
- Neurofibrosarcoma (neurogenic sarcoma) 96 649 651 654-655 837-839
- Neuroglia heterotopic 808-809
 - in teratomas 957 966 972
 - normal types of 803
 - reaction of to tumours 137-138

INDEX

- Neuroglia (*cont*)
 - tumours of (see *Gliomata*)
- Neuroma 846
- Neutrophil leucocytes in tumours 138-139
- Nickel as carcinogen 357-358 365
- Nicotine 47 872
- Nipple Paget's disease of 136 247-253
- Nomenclature of tumours, 9 18 205 321 643
- Notochord development of 918-919
 - tumours of 918-923
- Nuclei of tumour cells 41 131-135
- Nucleic acid in tumours 132
- Nucleoli of tumour cells 41 132
- Nutrition affected by tumours 25-27 144-145 203 310
- Occupation in relation to tumours 29 46 87 255-263 294 357 363-366 595 599 678
- Oculomotor nerve tumours of 829 839
- Odontoblasts 309-310
- Odontomes, 310 317-318
- Oestrogens affecting growth of tumours 103 142 245-246 589-590
 - in causation of tumours 48-53 630
 - produced by tumours 131 491 497-500 503 613 634
- Oestrous cycle and breast tumours, 50
- Oesophagus, adenoma of 387
 - angioma of 713
 - carcinoma of 71 74 81 82 94 165 178 387-390
 - cysts of 387
 - diverticula of 388
 - leiomyoma of 733
 - leucoplakia of 388
 - papilloma of 387
 - rhabdomyosarcoma of 755
- Oil cancer 29 34 248 259 598-599
- Oleic acid co-carcinogenic 31
- Oligo-astrocytoma 803 813
- Oligodendrocytes 803 813 814
- Oligodendroglioma 186 803 805 813 814 819 820
- Ollier's disease 671 710
- Omentum, angioma of 709
- Onkocytoma 348
- Oophoroma folliculare 489
- Opisthorchis 434
- Optic nerve angioma of 710
 - ganglioneuroma of 869
 - glioma of 807
 - meningioma of 719
 - neurofibromatosis of 835
 - retinoblastoma invading 891-892
- Organization of tumours 22 126
- Origin of tumours (see *Tumours mode of origin*)
- Ossification metaplastic (see *Metaplasia*)
- Osteitis, deformans 589 591 640 642 679
 - fibrosa 636-647
 - radium 678
- Osteo-arthritis 361 372 421
- Osteoblasts properties of 663
- Osteoclastoma 680-686
- Osteoclasts properties of 668

INDEX

- Osteoma 98 672-674
- Osteomyelitis carcinoma of sinuses 261 271
- Osteophytes with secondary tumours of bone 137
- Osteoplasia 136-137 244 588 589 591 592
- Osteosarcoma (Osteogenic sarcoma) 37 56-57 95-98 102 137, 168 218 220 669 677-683 688 690
- Ovary
 - adeno fibroma of 485
 - adrenal tumours of 503 507
 - arrhenoblastoma of 500-504 510
 - ascites with tumours of 485-486
 - Brenner tumours of 489-491 510
 - carcinoma of 487-489
 - age incidence of 81 487
 - in animals 94-98 510-513
 - metastases of 488-489
 - in bones 489
 - in Fallopian tube, 516-517
 - in liver 178 488 489
 - in lungs 178 489
 - in lymph glands 166 168 488
 - in uterus 188
 - social class and 88
 - squamous metaplasia in 488
 - structure of 166 487-488
 - veins invaded by 489
 - chorion-epithelioma of 985 991
 - classification of tumours of 483
 - cystadenocarcinoma of 487
 - cystadenoma of pseudomucinous 486-487 510
 - serous 483-486 510
 - dermoid cysts of 944-947
 - dysgerminoma of 504-506 510
 - epithelial tumours of 481-513
 - fibroma of 484 496 653
 - fibro-papillary tumours of 483-486
 - follicles structure of 481 482
 - follicular adenoma of 494
 - granulosa-cell tumours of 95 491-500 503 510-513
 - gynandroblastoma of 502-503 510
 - histogenesis of tissues of 481 509
 - histogenesis of tumours of 481-482 509-510
 - hormonal disturbances with tumours of 491 492 497-504 510
 - hypernephroma of 507
 - Krukenberg tumour of 405 408-409 425 482
 - luteal cysts of 991
 - luteal-cell tumours of 491 496 498 507
 - mesonephroma of 507-509
 - of phalanger 482
 - oophoroma folliculare of 489
 - papillary tumours of 116 166 483-487 510-513
 - psammoma-carcinoma of 166 487
 - secondary tumours of 178 242 376 405 408-409 425 430 482-483 507 531 532 539 912 991
 - secondary tumours mistaken for primary ones 408-409 425 482-483 985
 - seminoma of 504
 - structure of 481-482
 - teratoma of 486 506 943-947 972
 - theca cell tumours of 491-500

INDEX

Ovary (cont)

- tumours of in animals 94-98 510-513
- Oviduct tumours of in birds 97 101
- Oyster tumours of 99

Pacian corpuscles in teratomas 958

Paget's disease of bone 589 591 640 642 679

Paget's disease of nipple 136 247-253

Paget's disease of skin 110 287 290 597

Palate carcinoma of 298-299

glioma of 808

osteosarcoma of 689

rhabdomyosarcoma of 740-741

salivary tumours of 320 324

teratoma of 953

Pancreas

carcinoma of 443-451

age incidence of 81 443-444

argentaffin 417 447 451

causation of 446

cystic 447 710

diabetes with 448

diagnostic errors in 71 74 441 443 447-449

frequency of 443

in animals 94 95 96 99 445

metastases of 168 178 448-450

mode of origin 118-119 446

multiple 444 446

sex incidence of 81, 444

site of 444

structure of 446-448

veins invaded by 449

cystadenoma of 443 444

epithelial tumours of 443-451

experimental tumours of 46

heterotopic 396-397 446

islet-cell tumours of 450-451

lymphangioma of 711

secondary tumours of 178 242 303 376 430 463 785 991

squamous metaplasia in 126 446

Papilloma (see under particular organs)

Paradental residues 309-311

Paradoxical embolism 177

Paraganglioma 872 875

Paramoecia affected by carcinogens 43

Parasites in relation to tumours 57-60 195 (see also *Viruses*)

Parathyroid glands adenoma of, 636-641

carcinoma of 639 640

functionally related to pituitary gland 639

hyperplasia of 636 639

tumours of 636-641

Parotid gland (see *Salivary glands*)

Parovarium tumours and cysts of 482 507

Parthenogenesis 976

Peau d'orange 240

Pelvis of kidney (see *Kidney pelvis*)

Penis carcinoma of 88 596-598

in animals 96 265-266 597

INDEX

Penis (*cont*)

erythroplasia of 290 597
 Paget's disease of 248 288 597
 papilloma of 596 597
 phimosis of 597

secondary tumours of 465
 Pepper's syndrome 844 849 864
 Pericardium and pericardial cavity
 invaded by tumours 372
 misdiagnosis of tumours of 185 359-360 374
 secondary tumours of 183 185 242 372 374
 teratoma of 943 950-952
 tumours of 99

Perithelioma 462

Peritoneum and peritoneal cavity
 extension of tumours in 180 185
 misdiagnosis of tumours of 184
 pseudomyxoma peritonei 184 487
 secondary tumours of 161 180-185 242 374 408 485-486 972
 teratoma of 947 949
 tumour cells in ascitic fluid 181-182

Pernicious anaemia 397-398
 Phaeochromocytoma (see *Chromaffin tumour*)
 Phagocytosis by tumour cells 139 150
 Phalangeal ovary of 482

Phalanges
 chondroma of 671 674-675
 chondrosarcoma of 676
 secondary tumours of 463

Pharynx

carcinoma of 299-302
 age incidence of 81 299
 causation of 300
 diagnostic errors in 71 74 301 304
 in animals 94 306
 metastases of 171 301-302 304
 sex incidence of 81 89 299-300
 site of 299-300
 social class and 88
 spread of 301
 structure of 300-301

chondrosarcoma of 688
 lymphosarcoma of 766
 pituitary residues in 627-628
 teratoma of 953

Phenol red 44

Phosphatases in tumours 137 589 680
 Pia mater (see *Meninges*)

Pig tumours in 96 226 266 433 654 666 756 780 797 915 932
 Pigmented mole 899-904 914 915
 Pineal gland endocrine relationships of 821-822
 pinealoma of 820-822
 structure of 821
 teratoma of 185 821-822 953-954

Pitch cancer 259 294 598

Pituitary gland
 adamantinoma of 315 628-629
 adenoma of 624-626 639
 carcinoma of 626-627

INDEX

erus (cont)

carcinoma of corpus of (cont)
 tuberculosis and 534
 veins invaded by 533
 cervix precancerous lesions of 526-528
 chorion-epithelioma of (see *Chorion epithelioma*)
 endometriosis interna of 535
 endometrium of carcinoma of (see *carcinoma of corpus* above)

endometritis of 394
 hyperplasia of 52 124 497-500 534-536
 implantation of tumours in 188
 metaplasia in stroma of 543-544 754-755
 mixed tumour of 543-544 752-755
 neuroglial heterotopia in 753-754

epidermal metaplasia in 910
 fibroids of 52

fibromyosis of 729

ganglioneuroma of 852

hydatidiform mole of 936-939

leiomyoma of accompanying mixed tumours of uterus 752

accompanying ovarian tumours 497

accompanying uterine carcinoma 533 535 536

causation of 730 731

experimental 52 730

fat cells in 729-730

in animals 96

invaded by carcinoma 530 538 731

malignant 731-733

mode of origin of 119 729

ossification in 729

secondary tumours in 245 731

structure of 729-730

leiomyosarcoma of 173 731-733

lipoma of 729

melanoma of 910

mixed tumours of 139 542-544 752-755

neuroglial heterotopia in 753-754

papilloma of 522 535

pyometra with carcinoma of 530

rhabdomyosarcoma of 752-755

sarcoma of 530 538 542

secondary tumours of 242 245

Vagina carcinoma of 88 547-548

embryonic sarcomas of 747-749

epidermal metaplasia in 910

melanoma of 910

rhabdomyosarcoma of 747-749

secondary tumours of 176 241 465 532 540 548 990 991

Varicose ulcer carcinoma of 110 111 260

melanoma of 907

Veins invaded by tumours 152 157-160 170 172 298 303 343 372 389 430 431 435 436

449 459 552 533 541 578 603 604 611 612-613 622 632 640 672 677 693 721,

726-727 732 749 769 775-776 932 972

retrograde embolism in 176-177 465 991

tumours of 737

Venereal disease in relation to tumours 268 550 (see also *Syphilis*)

Vermiform appendix (see *Appendix*)

INDEX

- Virchow-Robin spaces extension of tumours in 161-163 450 909 914
- Viruses in tumour causation 58-60 120-121 195 198-199 473 781 819
- Viscosity of tumour cells 41 149
- Vitamin deficiency effects of 38
- Vitamins in tumours 143
- Vulva basal cell tumours of 272 552
- Bowen's disease of 552
- carcinoma of 88 96 110 266 548-552
- erythroplasia of 290
- glandular tumours of 552-553
- karyosis of 287 290 549
- leucoplakia of 110 123 287 290 549-551
- pigmented papilloma of 269
- secondary tumours of 176 465 540 990-991
- Walker rat tumour 140
- Walther nests 490
- Warts infective 268
- tar 30
- venereal 268
- Wilms's tumour 925-932
- Wolf tumours in 306
- Xanthofibroma 650
- Xanthoma 693 694 696
- Xeroderma pigmentosum 89 90 110 123 125 258 260 278
- Y rays as cause of tumours 35 56 258 260 271 492 510 781 796
- therapeutic response to of dysgerminoma 506
- of Ewing's tumour 687
- of myelomatosis 786
- of neuroblastoma 861 865-868
- of reticulum-cell sarcoma 686 687
- Yeast affected by carcinogens 43
- Zimmerman's pericytes 715
- Zondek Aschheim (see *Aschheim Zondek*)
- Zuckerlandl's bodies tumours of 872

the average or *mean age* but in most homogeneous groups of tumours the mean and modal ages do not differ by more than 3 or 4 years

Different kinds of tumours of course differ very greatly in their age incidence and even different kinds of carcinomas show decidedly different mean ages. Thus in the series of Table II, the mean ages at death of particular groups were as follows

TABLE V

Carcinomas	No. of cases			Mean ages in years
	M	F	Total	
Lung—	70	14	84	55.4
Cervix uteri	—	37	37	56.2
Ovary	—	18	18	56.7
Kidney	23	4	27	57.7
Breast	—	92	92	58.1
Renal pelvis and ureter	7	1	8	60.1
Large intestine	114	76	190	60.5
Corpus uteri	—	12	12	61.1
Larynx	10	1	11	62.2
Stomach	157	70	227	62.3
Bile ducts and gall bladder	25	33	58	63.6
Buccal cavity and pharynx	61	14	75	63.9
Bladder	27	10	37	64.3
Pancreas	28	14	42	64.8
Oesophagus	32	3	35	66.7
Prostate	40	—	40	71.8
Sundry	41	26	67	63.5
TOTALS	635	425	1060	62.0

The order of the tumours in Table V is closely similar to that of most other reported series of fatal carcinomas though the actual mean ages for particular tumours differ from series to series according to the age composition of the respective communities. Carcinomas of the lung, cervix, ovary, kidney and breast occur and kill at mean ages decidedly less than that of carcinoma in general, while carcinomas of the bladder, pancreas, oesophagus and particularly of the prostate occur and kill at average ages later than the general mean. A similar order of tumours obtains also in many reported series of non-fatal clinical cases the recorded ages of which are those of onset of symptoms or of diagnosis. Thus the large series of New York cases reported by Pack and Le Fevre shows the mean ages of renal, cervical, uterine, mammary and pulmonary carcinomas to be decidedly less than, and the mean ages of oesophageal, cervical and prostatic carcinomas to be decidedly greater than the average of all carcinoma cases. In Pack's and Le Fevre's series however the mean ages throughout are several years less than in those of Table V, partly because of the younger mean age of their population, partly because of the difference between clinically recorded ages and ages at death. This last matter requires further discussion.

(3) Ages of onset, of diagnosis and of death duration of tumours

The age of onset of most internal tumours cannot be determined. Not only are the first symptoms of many tumours insidious in onset, but the tumours are often already of long duration when the first symptoms appear. Indeed, it is far from unusual for primary growths to remain symptomless throughout their course producing their first signs by their metastases or being discovered unexpectedly at necropsy. The tumours most prone to do this include many carcinomas of the lung, kidney and stomach but all main classes of internal carcinomas afford similar instances. Although teratomas clearly take origin in early embryonic or foetal life, their clinical appearance is usually deferred for varying periods from childhood to old age, or they may be discovered only incidentally at necropsy. So also neuroblastomas and ganglioneuromas, nephroblastomas and other embryonic tumours, though arising in early developmental life, may not become clinically apparent until later childhood or adolescence. Many internal benign tumours, e.g. uterine myomas, remain symptomless and unsuspected for long periods. Clearly for all such tumours as the foregoing, the real mean ages of onset of the neoplastic changes cannot be deduced even approximately from the ages of symptomatic onset. The ages of onset of externally visible or palpable growths, or of those whose position is such that they usually occasion early symptoms, can be more accurately assessed. This applies to most carcinomas of the skin, breast, buccal cavity, oesophagus, pylorus, bile ducts and uterus and to many intracranial tumours. But plentiful exceptions occur even carcinomas of the breast are often quite large and clearly of considerable age when they are first noticed.

Age at diagnosis, or at admission to hospital which is given in many clinical series of cases clearly lacks precision. It depends arbitrarily on the very variable lag period between onset of first symptoms and the patient's seeking medical aid, on the diagnostic difficulties of the case and on the efficiency of the clinicians concerned. And as we have seen earlier in this Chapter in many classes of internal tumours many misdiagnoses are made by the most competent clinicians.

Age at death—the age recorded in necropsy and mortality statistics, is precise and definite. But in the latter, of course the value of the age records as of all other recorded details is limited by the degree of diagnostic error in the class of tumours considered, especially by the proportion of positive misdiagnoses erroneously included in that class. The ages at death of necropsy cases of proven nature are then the only absolutely definite and reliable age records in cancer.

The natural duration of tumours is for reasons already given often impossible to assess. Greenwood estimated the mean symptomatic durations in months of untreated carcinoma cases to be—for the breast 38.3, rectum 26.7, uterus 20.9, stomach 16.8, tongue and mouth 16.5, and oesophagus 12.0. But he was careful to point out that the precise times of onset of cancerous changes were unknown and that the probable order of reliability of the dates of symptomatic onset in this respect was—tongue, breast, uterus, rectum, oesophagus, stomach. The effect of treatment on duration, and therefore on final mean age, was exemplified



mortality statistics, they can be valid only between countries with similar standards of practice and registration. Most of the countries of Western Europe, of the English speaking parts of the British Empire and U S A are probably of nearly equal standards so that their mortality figures may be broadly comparable. Clearly, however, no two countries can be exactly comparable in this respect and the ways in which their standards diverge and the extent to which they diverge are unknown. Bashford long ago doubted the reliability of comparisons of the mortality figures of even the European countries and Hill in 1939 described comparisons of the mortality figures of different countries as "fundamentally of a dubious character". Between countries of widely different standards of medical practice and registration comparisons of tumour incidence as recorded in mortality figures must be quite unreliable, except perhaps as regards the most obvious kinds of external growths such as mammary and oral carcinomas. For this reason comparisons between the countries just mentioned, on the one hand, and those of Eastern Europe, the U S S R, Asia and S America, on the other, must be viewed with great caution.

As regards (b), we have seen that in modern civilized communities more than half of the cancer deaths occur at ages over 60 and more than a quarter of them at ages over 70. Clearly then communities differing only moderately in age distribution, especially as regards the proportion of persons in the later decades will differ very decidedly in tumour incidence. Young recently established communities, with relatively few old people will suffer from far less cancer than an old settled community with a high proportion of old people. Native communities with relatively low mean expectation of life, such as most of those of Asia, Africa and the Pacific will have relatively low cancer incidence. No valid comparisons of tumour incidence between different races, nations or other aggregates of people can be made unless their respective age compositions are known. These are known for most civilized communities of European origin, but not for the native communities referred to.

It is necessary to refer here to a hoary fallacy which though repeatedly exposed by Bashford, Wells, Cramer and others, is still voiced—namely, that "cancer is a disease of civilization" or that "cancer is rare in savage races". Since savage races have neither mortality statistics nor age composition statistics, comparison of the frequency of cancer in them with that in civilized races cannot be made. Moreover ample pathological and hospital records exist to show that tumours of all kinds do occur in all known races—that many of the kinds of tumours which are commonest with us are also common in native races, and that some tumours which are relatively infrequent with us are common in certain native races. The following recent papers are valuable sources of information regarding tumours in natives of India and Ceylon—Nath and Grewal (1935, 1937 and 1939), Khanolkar (1945) and Cooray (1944), of the East Indies—Bonne (1935), of China—Bercovitz (1941), of the West Indies—Hirtz (1940), of Nigeria—Smith and Elmes (1934) of South Africa—Strachan (1934) and of Negroes in America—Quinland and Cuff (1940). Other references to particular tumours are given in the Chapters of Part II.

Comparison of the mortality figures of various countries which possess reliable data shows that racial differences of susceptibility to cancer generally,

as follows: the expectation of life of a healthy woman 55 years old was 18.87 years, of a woman of 55 with untreated breast cancer 3.25 years, of a woman with breast cancer operated on under average conditions 5.74 years, and under the best conditions (with localized carcinoma and no involvement of lymph glands) 12.93 years.

Comment

Briefly then, ages of symptomatic onset and ages of diagnosis are indefinite figures which give only rough indications of the real ages of onset of tumours. Ages at death are definite figures, but the differences between them and the corresponding ages of onset vary greatly according to the natural durations of the tumours, their productivity of symptoms and the efficacy of treatment. These considerations though obvious enough are often overlooked in published papers. Any statistics dealing with age incidence should make clear what ages are referred to, should ensure that these are homogeneous in kind throughout the series and should indicate whether or not treatment may have affected the duration of the tumours.

(4) The cancer age

To what extent cancer is predominantly a disease of the elderly can be seen in Table II. This shows that people over 70 years old (5 per cent of the population) account for 27 per cent of fatal carcinomas; people over 60 (14 per cent of the population) for 60 per cent, and people over 50 (38 per cent of the population) for 84 per cent. i.e. about four fifths of all fatal carcinomas occur in the oldest one third of the community. This accords with the Registrar General's figures for cancer deaths in England and Wales in 1938 which show that nearly one half of the 68,600 cancer deaths were at ages over 65 years and about two thirds of them at ages over 60 years. We now know that cancer is mainly a disease of the elderly, not because senile tissues are 'predisposed' to cancer, as was once supposed, but because of the usually long latent periods elapsing between the application of carcinogenic stimuli and the development of tumours. Occupational and experimental tumours show that these periods often occupy large fractions of the life spans of the affected animals. The rapidly increasing liability to cancer with advancing age is of the utmost importance in comparing the incidence of tumours in different races, countries or communities and in estimating the trends of tumour incidence with the passage of time in the same community.

NATIONAL AND RACIAL DIFFERENCES OF TUMOUR INCIDENCE

In comparing the incidence of tumours in general or of particular kinds of tumours in two different peoples two preliminary questions already indicated must be asked: (a) Are their respective statistics comparable in reliability? and (b) Are their respective populations similar in age composition?

As regards (a) we have already seen that even the best mortality statistics are unreliable for most internal cancers and that the degree of unreliability must vary from community to community according to the standards of medical practice. Since most comparisons between different countries are made from their

trends in males and females, mentioned in paragraph (b) above over 90 per cent of male cancers are internal and difficult to diagnose while 40 per cent of female cancers are accessible and easy to diagnose Duffield and Di Mario concluded that 'much if not all, of the apparent increase in cancer mortality has resulted directly from improved diagnostic techniques and the increased opportunities for their use'

(d) *Efficiency of treatment* must also influence, to an unknown extent, the apparent trends of cancer mortality Improved surgical and radiational therapy must surely have caused some progressive reduction in the proportion of fatal cancer cases and to that extent must have masked the real incidence and trend of cancer Suppose that some highly efficacious method of treatment were to be introduced, then it would be possible for the real incidence of cancer to be increasing and yet for the mortality rates to show a sharp downward trend

(e) *Efficiency of prophylaxis against infective diseases* is important in modifying the incidence and trend of neoplastic diseases Decreased deaths from typhoid fever pneumonia tuberculosis and other preventable diseases mean a corresponding increase in deaths from "non preventable" diseases such as cardiovascular and renal disease and cancer From Canadian figures, Macklin (1932) concluded that cancer *was* increasing, especially in age groups over 60 "Excellent public health measures and high cancer rates are inseparable, at least for the present Those who point to the low cancer rates existing among primitive peoples, and who state that cancer is a disease of modern civilization, neglect to call attention to the fact that preventive medicine is itself a triumph of modern civilization'

Conclusion

There is no evidence that the real incidence of cancer as a whole is changing save in so far as the age compositions of populations change, or as people are prevented from dying of other diseases Hoffman and others who have believed that there has been a real and alarming increase of cancer in all civilized countries, have underrated the great degree of fallibility in the registered causes of death and the degree of improvement effected in these by improved methods of diagnosis

(2) Trends of incidence of particular tumours

The foregoing discussion of the trend of cancer as a whole has focused attention on the various factors which must be weighed in considering the trends of any disease or group of diseases It is doubtful, however, whether the trend of so vague a disease as cancer as a whole is worth ascertaining Much more important is it to ascertain whether particular kinds of tumours show distinct trends Clearly, for reasons already stated it is at present useless to attempt to discover the trends of any of the internal cancers the diagnosis of many of which is erroneous But of such tumours as carcinomas of the buccal cavity skin, breast and uterus there can have been but little improvement in diagnosis during recent decades, and comparison of their present mortality rates with those of earlier periods is legitimate This shows that in both Great Britain and USA of recent years, there has been a real increase of breast carcinoma, there has probably been a real decrease of carcinoma of the uterus, and that there

if such exist are slight. The age standardized cancer rates of different countries are closely similar. The relative frequencies with which the various sites are afflicted vary from country to country clearly because of differences of exposure to external carcinogenic stimuli resulting from peculiarities of custom, habit and occupation.

TRENDS IN TUMOUR INCIDENCE

It is pertinent to ask whether in a given community the incidence of cancer as a whole or of particular kinds of tumours has altered demonstrably with the passage of time. Let us clarify the several factors involved in answering the following familiar question:

(1) Is cancer increasing?

(a) *The figures used in the attempt to answer this question* are usually the mortality rates as estimated from death certificates in successive periods. We have already seen that these are subject to great error as regards nearly all kinds of internal tumours and that the aggregated figures for all kinds of malignant disease irrespective of errors of diagnosis of site are less than the real figures. Just how great this margin of aggregate error is or to what extent it may vary from period to period with improved methods of diagnosis and registration, we do not know.

(b) *Alterations in the age composition of the community* during the successive periods considered must be known and allowed for. If a population is ageing, i.e. showing increasing proportions of old people with the passage of time, then clearly cancer will be increasing in it. But this increase will be of little interest: it is only age standardized trends which are of real significance. To what extent the age standardized figures correct the impression given by the crude mortality figures is shown in the Registrar General's report for 1932, cited by Cramer. In that year the crude figures showed an increase of cancer mortality over that of the decennial period 1901-10 of no less than 93 per cent for males and 48 per cent for females, but correction for the change in age-composition of the population reduced these figures to 34 per cent and 3 per cent respectively.

(c) *Improvements in diagnosis and registration* clearly have an important effect on cancer mortality records and their apparent trends. It is only within recent years that many radiographic, endoscopic, biochemical and pathological methods of diagnosis have been introduced or perfected and that adventurous surgery has explored regions and diseases formerly regarded as beyond her bounds. All this has greatly improved and is still improving cancer diagnosis but no one can assess the exact degree of improvement. Many writers, e.g. Cramer, Dublin, Duffield and Di Mario have noted that the increase in age standardized cancer death rates during the last few decades has been mainly for cancer of internal sites and that there has been relatively little increase in rates for accessible easily diagnosed tumours. This difference strongly suggests that the increased rates for internal cancers are largely due to improved diagnosis. As Duffield and Di Mario pointed out this also explains the difference of the apparent cancer

contains much detailed evidence regarding differences of mortality rates from various kinds of cancer according to social class. The comparisons were made by assigning each occupation to one or other of five descending social classes and assessing the *standardized mortality ratio* (S M R) of each kind of cancer in each of the five classes. The S M R was estimated as a percentage ratio of the actual number of deaths in the particular class to the calculated standard number for the class estimated from its known age and sex composition. It is a measure of the relative liability of comparable samples of the classes to the particular tumour.

It was found that for cancers of the upper alimentary canal from mouth to pylorus the S M R's for males of the five descending social classes were 63, 80, 97, 109 and 129. When married women were grouped according to the social class of their husbands, they showed a similar class gradient for upper alimentary cancers. The factors responsible for the class gradient in cancer of the buccal cavity, oesophagus and stomach, are therefore almost as effective in the aggregate amongst wives of men engaged in the various occupations forming the social classes as amongst men actually engaged in the occupations, and it must be concluded that these factors are connected to a greater degree with the general economic circumstances, home life or dietaries which are associated with occupations than with the occupations themselves.

* Other sites which manifest an unmistakable social class gradient amongst males, tending to maximal levels amongst the unskilled classes, are the larynx, skin, scrotum and penis, which are sites exposed to external irritants. The mortality ratio for the larynx ranged from 60 for males of Class I to 143 for males of Class V, but it is significant that married women showed no significant social class gradient, thus suggesting that the factors responsible for the excess of cancer of this site amongst unskilled males are directly associated with occupation. For cancer of the skin on the other hand married women showed a similar class gradient to males, showing that peculiarities of occupation are by no means the only factors concerned.

Uterine cancer showed a class gradient from S M R of 65 for married women in Class I to 130 in Class V. Uterine cancer in single women, and vulval and vaginal cancer also showed a similar, but less pronounced, gradient. Cancer of the breast diminished from the higher to the lower classes (138, 116, 103, 84 and 82), so did cancer of the ovary (143, 116, 102, 77, 83). For single women, the class gradient for breast cancer was much less marked than for married women.

Cancer of the buccal cavity and pharynx showed a pronounced class gradient for males, the lower classes suffering most, but a less distinct gradient for females. "Either the type of occupation in itself or certain habits which are greatly influenced by social class amongst men but not amongst women must be important factors in the production of cancer of the buccal cavity and pharynx in the men. Cancers of the stomach and oesophagus showed pronounced class gradients in both men and women, the lower classes suffering most. Cancers of the intestine and of the bladder showed no significant class differences.

While the social gradients for accessible easily diagnosed tumours such as those of the breast, uterus, skin, and buccal cavity may be accepted without reserve, the large degree of error known to be present in the mortality records

has probably been little or no change in the incidence of carcinomas of the skin or buccal cavity (Cramer Duffield and Di Mario Bogen)

OCCUPATION AND CANCER

The association of particular kinds of tumours with certain occupations is sometimes too obvious to require statistical analysis e.g. chimney sweep's cancer cotton spinner's cancer aniline cancer of the bladder carcinoma of the lung in the miners of Schneeberg and Joachimsthal and osteosarcomas in the dial painters of New Jersey

However, apart from immediately obvious occupational associations of this kind statistical analysis shows significant occupational differences in the incidence of particular tumours or of cancer generally Thus the Registrar General's report on cancer deaths in England and Wales for 1930-32 showed general rates much higher than the average for furriers glass blowers tin and copper miners stevedores curriers leather dressers etc and rates much lower than the average for teachers clergymen retailers telephonists etc Or as an example of occupational differences of a particular kind of tumour the mortality rates from cancer of the buccal cavity and pharynx were much higher than the average in barmen furnacemen, dock labourers, horse drivers general labourers hotel keepers etc and much lower than the average in retailers clergymen, tram drivers railway officials agents and brokers teachers bank officials civil servants farmers etc Although these differences are statistically significant the occupational factors responsible for them are uncertain occupations are often difficult to classify with precision people change their occupations and as regards tumour causation occupation earlier in life is more important than that engaged in later and recorded on a death certificate

However, the many occupational differences revealed by analyses such as the Registrar General's afford hints of possible carcinogenic factors which are worth further statistical and experimental investigation It is important to emphasize here the great length of the latent period often intervening between the application of the carcinogenic stimulus and the eventual appearance of the tumour This makes it useless to look for the causes of human tumours in the occupations and habits of affected persons during the parts of their lives immediately preceding the appearance of their tumours The tumour of to day is often the consequence of stimuli applied 10 20 or 40 years ago Our medical histories and therefore our statistical data of tumour patients are often totally deficient in this respect detailed inquiry into the occupations and habits of the whole of the patient's previous life remote as well as recent is rarely undertaken Here is a great almost virgin field of research exploration of which by competent workers with a full knowledge of the problems involved must be undertaken if we are to sift out of our complex environment the carcinogenic factors which are yet unrecognized And the same applies to the elucidation of the causes of many other chronic diseases—blood dyscrasias hepatic degeneration and cirrhoses endocrine disorders and chronic renal and arterial disease

SOCIAL CLASS AND CANCER

The Registrar General's report dealing with occupational mortality for 1930-32

which shows the unexpected frequency with which multiple cases of cancer may occur in families of various sizes without there being any hereditary tendency "Usually, too only one part of the field is reported in medical literature, for notice is taken of the remarkable instances and no reference made to the cases in which no inheritance is apparent" (Hill)

One important statistical approach to the question of familial or inherited susceptibility to cancer of a given organ is to ascertain whether the immediate relatives of victims of the disease show it with greater frequency than the general population of comparable ages Detailed studies of this kind, carried out by Wassink in Holland and Waaler in Norway, and summarized by Cramer (1938 and 1942) and by Blank (1944) appeared to show that carcinoma of the breast, uterus and prostate did occur with abnormal family frequency Thus close female relatives of victims of breast cancer showed a decidedly higher incidence of breast cancer than could be accounted for by chance, but this did not apply to cancer of other organs while the close female relatives of sufferers from uterine carcinoma showed an abnormally high incidence of uterine carcinoma Carcinoma of the stomach showed a slight familial predisposition, but no pre disposition was apparent with carcinomas of the skin or lip Before drawing final conclusions from studies of this kind, further careful investigation is needed, and it must not be forgotten that near relatives are often exposed to similar environments

Another method of examining the possible influence of heredity in human tumours is to ascertain the tumour incidence in identical twins Great caution is needed, however in collecting and evaluating such information adequately authenticated cases are few, and instances of the occurrence of similar tumours in twins are much more likely to be reported than instances of non concurrence Failure to appreciate this misled McFarland and Meade into concluding that tumors occurring in homologous twins seem always to be similar, symmetrical and simultaneous Versluys however, critically examining this question, found that the occurrence of a tumour in one twin only was more frequent than concurrent tumours in both twins, and that dissimilar tumours in twins were commoner than similar ones whence he concluded that exogenous factors were more important than genetic factors in the genesis of tumours in twins Weitz also adduced evidence that concordant cancer in identical twins is exceptional Of course, with diseases of known familial character, such as retinoblastoma, polyposis and xeroderma monozygotic twins are very likely to develop similar simultaneous tumours, but with these special exceptions, the pathology of twins gives little evidence of any strong genetic predisposition to cancer

Kennaway and Kennaway discussing (a) the total incidence and (b) the incubation period of particular kinds of cancer in man, point out that more intense carcinogenic stimuli are required to shorten (b) than to increase (a), and that (b) particularly is influenced by genetic factors Thus the mean age at death from chimney sweeps scrotal cancer a disease probably due wholly to external carcinogens and devoid of any genetic predisposition, is about the same as it is in the general population although the liability to this disease among sweeps is enormously greater than in most other occupations But forms of cancer in which a familial factor is concerned (familial polyposis, xeroderma pigmentosum,

of gastric, ovarian, and many other visceral tumours, should engender caution in accepting the apparent social gradients for these

SEX AND CANCER

Apart from the organs of reproduction and the breast many other organs show pronounced sex differences of tumour incidence. These will be discussed in the Chapters of Part II, only a few examples will be given here.

The Registrar General's report 1930-32 contains the following figures

TABLE VI

Site of carcinoma	Deaths	
	Males	Females
Lip - - - - -	849	20
Tongue - - - - -	3 225	217
Mouth and tonsil - - - - -	1 706	143
Pharynx - - - - -	1 075	221
Stomach - - - - -	18 976	9 243
Bladder - - - - -	2 668	675

The preponderance of males in each of these groups of tumours was even more than shown because the population contained an excess of females.

Mortality figures are too unreliable for assessing the sex ratio of most kinds of internal cancers. These are better estimated from large series of *proved* clinical or necropsy cases, such as my series of Table V above. Since this series was from a hospital which contained approximately equal numbers of male and female beds, the ratios shown may be taken as approximate measures of the relative liabilities of men and women to the diseases in question. It will be seen that Tables V and VI show roughly similar sex ratios for the tumours listed in both. Lymphosarcoma, leukaemias and Hodgkin's disease also show a pronounced preponderance in males (see Chapter 49). Notice that nearly all kinds of malignant tumours of viscera other than the reproductive are commoner in men than in women. Yet the total number of female deaths from cancer exceeds the total number of male deaths. In England and Wales in 1938, the female and male deaths from malignant disease were recorded as 35 913 and 32 692 respectively. This is because of the much greater frequency of uterine and mammary cancer than of cancer of the male reproductive organs.

HEREDITY AND CANCER

The inheritance of a predisposition to cancer is obvious in cases of familial retinoblastoma, multiple polyposis of the large intestine or xeroderma pigmentosum and rarely a family such as that described first by Wirthin and later by Hauser and Weller shows so many members in successive generations with some other particular kind of cancer that an inherited predisposition cannot be doubted. Most supposed 'cancer families' however exemplify only the laws of chance. Crimer rightly recalled a table of Bashford's

- PACK, G T**, and **LE FEVRE, R G** (1930) The age and sex distribution and incidence of neoplastic diseases at the Memorial Hospital, New York City *J Cancer Res* **14** 167 (A good example of analysis of a hospital series)
- Quinland W S** and **Cuff J R** (1940) *Arch Path* **30** 393
- REGISTRAR GENERAL S DECENNIAL SUPPLEMENT, ENGLAND AND WALES, 1931**
Parts I and IIa (1936 and 1938) (A valuable example of detailed analysis of mortality figures)
- Registrar General's Statistical Review of England and Wales 1938 and 1940
- Smith E C** and **Flmes B G T** (1934) *Ann Trop Med and Parasit* **28** 461
- Strachan A S** (1934) *J Path Bact* **39** 209
- Versluys J J** (1934) *Z Krebsforsch* **41** 239
- Warthin A S** (1925) *J Cancer Res* **9** 279
- Weitz W** (1936) *Die Vererbung innerer Krankheiten* Stuttgart
- WELLS, H G** (1927 and 1931) Cancer statistics as they appear to a pathologist *J Amer Med Assoc* 1927 **88** 399 and 477 and *Amer J Cancer* 1931 **15** 1919 (Important papers on the fallacies of cancer statistics)

the family "G" of Warthin, and some cases of cancer of the breast) lead to death at average ages much earlier than do the same forms of cancer in the general population

Blank (1944) has given a useful recent review of the genetic aspects of cancer and has particularly stressed the point with which the present chapter opened namely, that 'cancer is not a unit disease'. Tumours of different sites and types differ in their genetic behaviour'. And again 'we must inquire separately for each tissue and type of the disease whether any hereditary factors direct or indirect are involved in a specific form of the malady'

The available statistical and experimental evidence shows clearly I think that while an inherited predisposition to particular kinds of tumours is sometimes discernible and is in occasional special instances paramount by far the larger number of human cancers is due to carcinogenic chemical or other stimuli which are probably effective in most adequately exposed individuals whatever their genetic inheritance

REFERENCES

- BASHFORD E F, and MURRAY J A (1905) The statistical investigation of cancer *Imp Cancer Res Fund Sci Rep*
 Bashford E F (1908) *Imp Cancer Res Fund Sci Rep*
 Bercovitz N (1941) *Cancer Res* 1 154
 Blank F (1944) *Arch Surg* 49 301
 Bogen E (1935) *Amer J Publ Health* 25 245
 Bonne C (1935) *Amer J Cancer* 25 811
 Cleland J B (1942) *Med J Austral* 1 579
 Cooray G H (1944) *Indian J Med Res* 32 71
 CRAMER W (1937) The importance of statistical investigations in the campaign against cancer *Amer J Cancer* 29 1
 Cramer W (1938) *Brit Med J* 1 829
 Cramer W (1942) *J Amer Med Assoc* 119 309
 Crockett C V (1943) *Med J Austral* 11 473
 Dublin L I (1936) *2nd Internat Congress against Cancer* 1 483
 Duffield T J and Di Mario M (1941) *Cancer Res* 1 413
 GREENWOOD M (1926) The natural duration of cancer *Rep Pub Health and Med Sub Lond* No 33 (An interesting example of the statistical complexities of a seemingly simple subject)
 Hartz P H (1940) *Amer J Cancer* 40 355
 Hauser I J and Weller C V (1936) *Amer J Cancer* 27 434
 HILL A B (1939) *Principles of Medical Statistics* London (An excellent book which should be read by all pathologists and clinicians)
 HOITMAN F L (1915) *The Mortality from Cancer throughout the World* Newark New Jersey
 Kennaway F L and Kennaway N M (1944) *Yale J Biol Med* 17 139
 Khanolkar V R (1945) *Indian J Med Res* 33 299
 LAND-CLAYTON J E. (1924 1926 and 1928) Cancer of the breast and its surgical treatment *Rep Pub Health and Med Sub* London 1924 No 28 1926 No 32 and 1928 No 51 (Valuable statistical analyses of the subject)
 Macklin M T (1932) *Amer J Cancer* 16 1193
 McFarland J and Meade T S (1932) *Amer J Med Sci* 184 66
 NATH V., and CREWAL, R. S (1935 1937 and 1939) "Cancer in India" *Indian J Med Res* 1935 23 149 1937 24 633 and 1939 26 785

in their proneness to tumours in general, and to tumours of specific kinds. Considering only animals of comparable ages, guinea pigs and rabbits develop tumours much less frequently than rats or mice. Pigs and sheep less frequently than other domesticated animals, and cats less frequently than dogs.

TUMOURS IN MAMMALS

(1) Primates

Tumours of primates are of course of special interest for comparison with their human counterparts, but very few examples have been reported. In Ratcliffe's large series of animals (1933), primates had the lowest incidence of tumours of all mammals. This was clearly due in great part to the ages of the animals, for the average exhibition period of all the captive primates was very low as compared with other mammals, and the few tumour bearing monkeys were all elderly. The malignant tumours included two adenocarcinomas of the pancreas, an epidermoid carcinoma of the cardia of the oesophagus, and a fibrosarcoma of the ulna, all in Old World monkeys. In 1940 Ratcliffe also reported renal adenocarcinomas in four members of one family of rhesus monkeys. Engle and Stout saw carcinoma of the prostate in an old macaque, and Steiner *et al* two instances of carcinoma of the tongue in monkeys.

(2) Dogs

Tumours are very common in middle-aged or old dogs, and in structure and behaviour many of them closely resemble, while some differ in instructive ways from their human counterparts. The following tabular summary of 204 canine tumours collected by Dr H B Rudduck of Melbourne and studied microscopically by me, indicates the relative frequency of the growths encountered. (Some of these were reported in 1938.)

The figures of Sticker, Murray, Feldman, Antoine *et al* and others also, show the most frequent canine tumours to include fibro adenomas and carcinomas of the breast, papillomas and carcinomas of the skin, carcinomas of the oral cavity and pharynx, melanomas, testicular tumours, leiomyomas and lymphosarcomas. Carcinomas of the gastro intestinal tract are extremely rare, and those of the other internal viscera not common, the least uncommon sites being thyroid, ovaries, bladder and prostate. The infrequency of alimentary and other visceral tumours in dogs is certainly not wholly attributable to their remaining undiscovered. Rudduck's and my specimens were from a nearly consecutive series of surgical and necropsy cases, in which deliberate search was made for tumours of all kinds, yet only one example of gastro intestinal tumour, a carcinoma of the cardia, was found. As in Antoine's series, no special proneness of any particular breed of dog to any particular tumour was noticed. Tumours which were frequently multiple in the affected animals included mammary fibro adenomas (5 cases), sebaceous adenomas (2 cases), adrenal cortical adenomas (bilateral in both cases), carcinoma of the breasts (5 cases), carcinoma of the liver (2 cases), papillary carcinomas of the ovaries (bilateral in both cases), melanomas (7 cases), and tumours of the testes (10 cases).

CHAPTER 6

TUMOURS IN ANIMALS

THE OCCURRENCE of particular kinds of tumours in animals will be referred to in the respective chapters of Part II. Here a brief outline of the main tumours occurring spontaneously in different classes of animals is given and their transplantation and other experimental methods of studying their properties are discussed. Much of value for human pathology is yet to be learnt from the study of animal neoplasms. More use should be made of the pathological material passing through the hands of veterinarians, breeders and slaughtermen, most of which is wasted. Sucker (1902) was one of the first to attempt a comprehensive survey of cancer in domestic animals, but his outline contains little pathological detail. Murray's papers (1908) are an important early contribution to the scientific study of animal tumours, and the monographs of Fox (1923) and of Feldman (1932) and the papers of Cramer (1932) and Ratcliffe (1933) are the best general accounts.

THE AGE DISTRIBUTION OF ANIMAL TUMOURS

In assessing the relative frequency of any particular kind of tumour, or of tumours in general, in different species of animals, the ages of the animals examined are of prime importance. Most spontaneous tumours in animals, as in man, occur in middle-aged or elderly animals. Thus in Sucker's series, more than two thirds of the horses with carcinoma were over 10 years old, and about two thirds of the dogs with carcinomas were over 6 years old. Of 204 dogs with tumours (of all kinds) examined by Rudduck and myself, the ages of 170 were known; of these 147 (86 per cent) were over 6 years of age. Of 39 sheep with tumours, examined by Feldman, 21 were designated old or aged. Mice with spontaneous tumours are usually at least eighteen months or two years old, and rats with tumours are usually between 2 or 3 years old. The increasing incidence of tumours with increasing age in all genera of both mammals and birds is strikingly shown in Ratcliffe's records.

Clearly then, tumours will be found much less frequently in animals which are often slaughtered for food at relatively early ages, such as sheep, cattle and pigs, than in domestic pets, such as dogs and cats, which often survive into old age. In mice, rats, guinea pigs and other laboratory animals, which are often under close observation for long periods, such tumours as occur will be found relatively frequently. It is impossible to estimate the frequencies of tumours in wild animals, because their ages are unknown, but that all species are probably susceptible to tumours is shown by the observations of Fox, Ratcliffe and others on neoplasms in captive animals.

However, when due allowance has been made for the relative differences of the proportions of the normal life spans attained by the several species of domestic and laboratory animals, it is clear that these species do differ intrinsically

(3) Cats

Tumours are decidedly less frequent in cats than in dogs. The commonest sites are the breast and skin. Rudduck and I studied 8 tumours from cats—2 adenocarcinomas of the pancreas, and one case each of adenocarcinoma of the liver, basal cell carcinoma of the skin, fibrosarcoma of skin, neurogenic sarcoma of skin, chondrosarcoma of the humerus, and angiomas of the liver.

(4) Horses

Tumours are more common in horses than in other ungulates of corresponding ages. The commonest sites of carcinomas are the skin, penis, vulva, nasal cavity and sinuses, conjunctiva, oral cavity and kidney. Tumours of the breast are relatively infrequent. Adenomas of the thyroid, leiomyomas of the alimentary canal and lipomas are not uncommon. Cutaneous melanomas are frequent, especially of the tail or perineal regions of old grey animals. Squamous cell carcinoma of the cardia is well known. Teratomas of the testis, not infrequently multiple and bilateral, are more frequent in the horse than in any other species. Lymphoid tumours appear to be less common than in other mammals. Rudduck and I studied the following tumours from 25 horses—papillary squamous cell carcinoma of the conjunctiva 13 cases, teratomas of the testes 5 cases, and one case each of squamous carcinoma of the penis, squamous carcinoma of the vulva, carcinoma of the breast, carcinoma of the ovary, adenocarcinoma of the thyroid, neurofibroma of the skin, and fibrosarcoma of the skin.

(5) Bovines

The commonest tumours of cattle are squamous carcinomas of the conjunctiva, carcinomas of the skin of the udder, lymphosarcomas and uterine myomas. Carcinoma of the uterus, ovary, liver, rumen, or thyroid are less common, carcinomas of the true stomach, intestines or mammary gland are rare. Tumours of the adrenal cortex are well known. Rudduck and I examined 5 tumours from cows—3 squamous carcinomas of the conjunctiva, a squamous carcinoma of the perineum, and an adenoma of the adrenal cortex.

(6) Sheep

Epithelial tumours are relatively rare—the two most frequent sites are the adrenal glands and the liver (Feldman). Lymphoid tumours and uterine leiomyomas occur. Rudduck and I saw the following three tumours in sheep—a chondrosarcoma, a lymphosarcoma and a papilloma of the gall bladder.

(7) Pigs

Epithelial tumours are rare. Melanomas, leiomyomas of the uterus and lymphosarcomas are not uncommon. The commonest tumour of swine is embryonic nephroblastoma usually in young animals and sometimes multiple and bilateral. This tumour appears to be more frequent in the pig than in any other mammal.

TABLE

TYPES OF TUMOURS	No of dogs	Total
<i>Benign epithelial tumours</i>		
Fibro adenoma of breast - - - - -	17	
Papillary cystadenoma of breast - - - - -	2	
Papilloma of skin - - - - -	4	
Sebaceous adenoma of skin - - - - -	4	
Cystic hydradenoma of skin - - - - -	1	
Ceruminous adenoma - - - - -	1	
Adenoma of adrenal cortex - - - - -	2	
Adenoma of thyroid - - - - -	1	32
(6 cases of adenomas of the third eyelid all from young cocker spaniels are omitted as they are probably only inflammatory hyperplasias)		
<i>Carcinomata</i>		
Skin - - - - -	23	
Breast - - - - -	15	
Tonsil - - - - -	10	
Alveolus of the jaw - - - - -	2	
Liver - - - - -	6	
Ovaries (papillary 2 granulosa 1) - - - - -	3	
Other (thyroid cardia pancreas lung eyelid prostate salivary bladder) - - - - -	8	67
<i>Tumours of testis</i>		
Interstitial-cell tumours - - - - -	16	
Seminoma - - - - -	7	
Rete or Sertoli cell tumours - - - - -	4	27
<i>Melanoma</i> (malignant 11 benign 6 doubtful 5) - - - - -	-	22
<i>Benign non epithelial tumours</i>		
Leiomyoma - - - - -	6	
Fibroma - - - - -	2	
Lipoma - - - - -	2	
Angioma - - - - -	2	
Basophil-cell tumour (see Chapter 51) - - - - -	2	
Chondroma - - - - -	1	15
(16 cases of single or multiple lymphoid growths in the spleen are omitted because doubtfully neoplastic)		
<i>Malignant non epithelial tumours</i>		
Lymphosarcoma - - - - -	16	
Osteogenic sarcoma - - - - -	6	
Fibrosarcoma - - - - -	6	
Angiosarcoma - - - - -	2	
Leukaemia - - - - -	2	
Chondrosarcoma - - - - -	1	
Other sarcomas - - - - -	7	40
<i>Carcinoma of thyroid</i> - - - - -	1	1
TOTAL - - - - -		204

Squamous carcinoma of the skin is uncommon. Rudduck and I examined a subcutaneous lipoma from a parrot, a subcutaneous myxoma from a parakeet, and a papilloma of the claw base from a magpie. The filterable sarcomas of fowls form a distinct and peculiar class (Chapter 4). Most avian tumours are not transmissible by filtrates.

TUMOURS IN THE LOWER VERTEBRATES

Records of neoplasms of the cold blooded vertebrates are relatively scanty. Reports of piscine tumours are more frequent than those of reptilian or amphibian—probably because of the wholesale capture and examination of fish as food. Sufficient records exist to show that fish are subject to a great variety of neoplasms, and to show that, were reptiles and amphibians of the same economic importance as fish, tumours would probably be found as frequently in them also.

(1) Fish

In 1904 Bashford and Murray referred to 7 examples of tumours in fish, in 1929 Takahashi collected 142 examples, and in 1933 Haddow and Blake reviewed reports of 174 piscine tumours and added 6 personally studied examples. Of the total 180 specimens, 114 were benign osteomatous or chondromatous tumours and 2 others were osteosarcomas. Other tumours included fibroma, lipoma, angioma, rhabdomyoma, soft tissue sarcomas, carcinomas of the mouth and gill region, melanomas, and ganglioneuromas. Visceral carcinomas were rare. Many different species of fish were affected—teleosts, as might be expected, easily preponderating.

In addition Gordon and Smith (1938) have made detailed studies of peculiar melanotic growths in hybrid fish, and Lucke (1942) has given an admirable account of subcutaneous neurinomas in 76 fish from 3 species of the snapper family.

(2) Amphibians

In his studies of adenocarcinomas of the kidneys of leopard frogs Lucke (1934) gave also a valuable review of previously reported tumours in amphibians. These included—in frogs, adenomas and adenocarcinomas of the skin glands, adenocarcinomas of the kidneys, sarcomas of the extremities, a carcinoma of the ovary, and a fibroma of the mouth—in salamanders two fibromas of the feet, and a carcinoma of the testis—and, in a triton, a carcinoma of the skin glands. Several of these tumours were reported, along with excellent figures by Murray (1908). Lucke (1937) has reported a myxosarcoma of the dorsal fin of a tadpole. Briggs successfully transplanted Lucke's renal adenocarcinoma of frogs to various sites in tadpoles. A carcinoma of a frog's liver is depicted in Fig. 196, Chapter 24.

(3) Reptiles

Lucke (1934) reviewed records of 11 reptilian tumours, namely a fibroma in a python, carcinoma of the ovary in a python, three cases of multiple papillomas of the skin in lizards, multiple enchondromas in a monitor, carcinoma of

(8) Rabbits

Spontaneous tumours in rabbits are infrequent. By far the commonest are adenomas and adenocarcinomas of the uterus (Polson Fardeau Burrows). Next in frequency are embryonic renal tumours and lymphosarcomas and other sarcomas. All other kinds of tumours are rare.

(9) Guinea pigs

Tumours are extremely rare—less than a score have been reported (Twort and Twort, Maury). These have included carcinomas of the breast, sarcomas and ovarian and adrenal tumours.

(10) Rats

Tumours of many kinds occur frequently in rats (Bullock and Curtis, Curtis *et al.* Ratcliffe 1940, Wright *et al.*). The commonest of these include benign fibro adenomas of the breast, fibromas and fibrosarcomas of the skin, lymphosarcomas, carcinomas of the uterus and benign thymic tumours. Carcinomas of the skin and breast are much less frequent than in mice. Embryonic renal tumours, usually in young animals, are relatively frequent. Osteogenic sarcomas are well known. Sarcomas of the liver associated with parasitic cysts constitute a special class (see Chapter 4). Curtis *et al.* found that different breeds of rats showed different incidences of particular tumours: one breed had many thymic tumours, another breed many mesenteric sarcomas, and another breed many mammary, uterine and skin tumours. The mammary fibro adenomas of rats are transplantable and this has proved of great value in elucidating the composite neoplastic character of these growths (see below).

(11) Mice

It is necessary only to mention the well known mammary, cutaneous, pulmonary and lymphoid tumours of mice and to refer to Murray's classical paper on mouse tumours and to the many papers of Slye, Holmes and Wells for further information. As in other domestic animals, alimentary carcinomas are rare. Different pure strains of mice differ very greatly in the spontaneous incidence of particular tumours, so that in carrying out any experiments on carcinogenesis it is of prime importance to ascertain the natural tumour incidence of untreated mice of the breed used. Many fallacious or doubtful interpretations of experimental results have been made through neglect of this obvious requirement.

TUMOURS IN BIRDS

The commonest spontaneous tumours of fowls and probably of many other birds also are lymphosarcomas and leukaemias (well summarized by Feldman, Chapter 14), carcinomas of the ovary or oviduct (Joest and Ernesti, Eber and Kriegbrum) and adenocarcinomas of the intestine. Embryonic renal tumours, leiomyomas of the alimentary canal or oviduct, and various types of sarcomas are also well known. Ratcliffe (1933) found that renal adenomas or adenocarcinomas were frequent in one species of parakeet. There have been several reports of gliomas of the brain in fowls and other birds (Belmonte, Jungherr and Wolf).

considerations are therefore irrelevant. Confirmation of this important principle has been the major result of the study of transplanted tumours.

Since tumour transplants often act as antigens in unrelated animals of one species, it is not surprising that heterologous transplantation between different species is rarely successful. Many early attempts were made to transfer human tumours to animals, but with no genuine successes. That such transference is not necessarily impossible under special conditions, however, is suggested by Greene's findings (1942), that human sarcomas and carcinomas may survive successive passages in the aqueous cavities of the eyes of guinea pigs and rabbits. More successful hetero-transplantation has occasionally been achieved between animals of closely related species. Fujinami's myxosarcoma of the fowl is transferable to ducks, and an Ehrlich mouse carcinoma can be transplanted to rats.

The immunity reactions to foreign cells or proteins evoked by tumour transplants limit the value of these in research. If transplantable tumours are used in a research, as for example to study the effect of a particular treatment on a large number of animals all carrying similar tumours, then non specific immunity reactions must be minimized by using a closely inbred homogeneous strain of animals and a tumour which has arisen in that strain. Otherwise, irregularities of natural and acquired resistance, corresponding to genetic and antigenic differences in the test animals will vitiate the results. The complexity of the serological problems created by the use of transplantable tumours in a non homogeneous strain of animals is well presented in a paper by Gorer (1938). For these reasons transplantable tumours are now much less in favour than formerly and experimentalists prefer whenever possible, to use spontaneous tumours or tumours evoked by chemical or other carcinogens. Certain special experiments in which tumour transplantation has proved of value in elucidating particular problems may now be outlined.

(2) The study of metastasis using transplanted tumours

While many of the problems of metastasis can be studied as well with spontaneous or induced tumours as with transplanted ones, for some purposes the latter are preferable. Thus, by intravenous injections of finely divided transplantable tumours, disseminated growths may be obtained in the lungs, and several workers have used this method to study the fate of tumour emboli following their arrest in the pulmonary vessels (references by Willis, 1934). Similar experiments using ascitic fluid containing tumour cells, were performed by Wibeau and by Warren and Gates, and Eisen obtained pulmonary growths by intravenous injections of emulsions of a mammary adenocarcinoma in rats.

Several workers (cited by Willis, 1934) have used large batches of animals bearing transplanted tumours to investigate whether or not injury or manipulation increases metastasis. The results have suggested that while rough manipulation or massage does aggravate dissemination, careful excision or incision of the tumours has little or no effect. For reasons already given, however, it is preferable that spontaneous or induced tumours should be used in such experiments.

The claims of Blumenthal, Gross and others, that tumours could be evoked in mice and rats by injections of blood, exudates and cell free material from

the foot in a tegu, adenoma of the thyroid in a turtle, adenocarcinoma of the stomach in a turtle sarcoma of the heart in a turtle and Scott's case of sarcoma of the liver in a crocodile with metastases in the heart and cerebellum Ratcliffe (1935) saw adenocarcinoma of the pancreas in a snake

TUMOURS IN INVERTEBRATES

Very few instances are recorded White dissected a large number of honey bees and found only one tumour, a lobulated fibroma of the thorax possibly of nerve sheath origin Smith described a large pedunculated mesenchymal tumour attached to the pericardium of an oyster and found two other reports of tumours in molluscs—one closely similar to his own and the other a pedunculated adenofibroma of the pallium of a mussel

THE EXPERIMENTAL TRANSPLANTATION OF TUMOURS

Towards the close of last century it was discovered that some of the tumours of animals could be transferred by grafts to animals of the same species, and that some of these transplantable tumours could be propagated from animal to animal for an unlimited number of transfers Such easily propagable tumours were eagerly sought after many of them were named after their discoverers, e.g. Jensen mouse carcinoma, Jensen rat sarcoma Flexner Jobling rat carcinoma, Brown Pearce rabbit tumour, and study of the behaviour of transplantable tumours engrossed a large part of the energies of cancer research For details of this work, consult the Reports of the Imperial Cancer Research Fund Nos 2 to 5 (1905-1912) especially the monographic account by Bashford *et al* (1908), and the excellent review by Woglom (1929)

(1) The limited value of transplantation experiments

It is now clear that the value of transplanted tumours in cancer research is limited The hope formerly strongly held by many workers that these tumours would lead to important discoveries in the subject of tumour immunity is now seen to have been a vain one The very phenomena which aroused this hope are those which place strict limits on the value of researches with transplantable growths A brief summary of the relevant facts is necessary

Early workers with transplantable tumours soon noticed irregularities in the success of grafts some grafts took while others under identical conditions failed These differences were ascribed correctly to differences in host resistance It was found that animals in which grafts had failed or had retrogressed after an initial take were resistant to further grafts the hope was raised that elucidation of the nature of this resistance might lead to practical methods of tumour prophylaxis and therapy Then however it was found that resistance to tumour transplants could be produced equally well by inoculations of normal homologous tissues especially embryonic skin The resistance so conferred had no effect on an existing spontaneous tumour or on the inability to develop one This resistance whether natural or induced was indeed only a general resistance against foreign tissue grafts not against neoplastic cells in particular Spontaneous tumours consisting of a creature's own tissues cannot act as antigens and serological

brought about by the epithelial parenchyma" Foulds noted "the close resemblance between the fowl carcinoma and mixed tumours of the human salivary glands", and rightly concluded that "in this type of mixed tumour, only the epithelial component is neoplastic"

In this connexion, the common mammary fibro adenomas of dogs are of peculiar interest. In these tumours bone and cartilage are common, e.g. in 7 of the 17 dogs in Rudduck's and my series, and in many of those reported by Schlotthauer (1940). While spuriously cartilaginous appearances are often produced in these tumours by inclusion of isolated epithelial cells within secretory products or hyaline stroma, true cartilage and bone, the result of metaplasia in the connective tissue of the tumours, also occur frequently. But, as we have already seen, this connective tissue is not a simple stroma but a truly neoplastic component of a mixed tumour. Hence, bone and cartilage derived from it must also be neoplastic. The occasional osteogenic sarcoma of the breast such as Schlotthauer's case 7, doubtless always arises from neoplastic bony tissue developed by metaplasia in the fibromatous component of a fibro adenoma. It would therefore be of special interest to ascertain whether any of the canine fibro adenomas could be transplanted, and, if so, to study the behaviour of their components in successive passages.

Mention must be made here also of a subject which is more fully discussed in Chapter 8, namely, the apparently sarcomatous change which has been described as occurring in the stroma of serially transplanted tumours. Haaland's classical account (1908) gives the fullest description of the changes observed, with many excellent microphotos but, in my opinion even these fail to exclude the possibility—indeed they even suggest the probability—that the supposed sarcomatous tissue may have been anaplastic diffuse carcinoma.

EXPERIMENTAL INVESTIGATIONS OF FACTORS INFLUENCING TUMOUR GROWTH

Spontaneous, induced or transplanted tumours in animals afford suitable material for controlled studies of factors influencing tumour growth and for controlled tests of agents of alleged therapeutic value. Alas a great proportion of the published studies of this kind are valueless, because of inadequacy of controls, insufficient appreciation of the wide limits of spontaneous variation in the behaviour of untreated tumours, variations related to age, nutrition, general health of the animals and doubtless many other obscure factors and the use of unsuitable tumours e.g. tumours with a high degree of natural variation of growth rate or a high proportion of spontaneous retrogressions. Reliable research in this field cannot be carried out by novices but in the hands of the experienced using pure strain animals bearing tumours the behaviour of which is thoroughly known, valuable results are obtainable. A further important principle is that results obtained with one kind of tumour must not be assumed to apply to other tumours without direct verification.

Voegtlin (1937) has given a useful summary of the enormous amount of work directed to discovering the effects on tumour growth of various nutritional, hormonal and metabolic factors. Conflicting claims have been advanced as to the influence of general nutrition particular proteins, amino acids, carbohydrates,

animals bearing transplantable tumours, have been shown by other workers (e.g. Flaks, Wagner) to depend on the transfer of disseminated tumour cells. Under suitable conditions then transplantation of tissue might afford a useful biological test for the presence of disseminated microscopic tumour deposits. Furth and Kahn found that a single leukaemic cell, isolated by means of a micro pipette sufficed for the transmission of mouse leukaemia. They showed also that cell free material from leukaemic mice or crushed leukaemic cells would not transmit the disease, so that unlike fowl leucosis mouse leukaemia can be transferred only by means of intact malignant cells. Kahn and Furth found also that a benzpyrene mouse sarcoma could be transmitted with 50 cells.

Transplantable tumours show individual peculiarities of metastasis and can be used to elucidate experimentally some of the factors influencing the frequency and distribution of metastases. One of the most interesting experiments of this kind was that of Foulds on the Brown Pearce rabbit tumour. Metastases from transplants of this tumour occurred frequently in the adrenals kidneys and eyes and less frequently in the liver and lungs and a similar distribution of disseminated growths developed following intravenous inoculation. But in animals vitally stained by repeated injections of trypan blue remarkable departures from the usual distribution of metastases were observed the spleen liver and lungs were now the commonest metastatic sites. Evidently vital staining had diminished the normal relative infertility of these organs as soils for metastasis. This experiment suggests a promising field of future research.

(3) The study of composite tumours by transplantation

If a composite or mixed tumour can be transplanted this affords a possible means of segregating or selecting its components and studying their behaviour separately. This has proved possible with the mammary fibro adenomas of rats (Robinson and Grauer, Heiman and Emge). Heiman and Emge found that the fibromatous component can be obtained in pure form by repeated transfer and that this component may eventually undergo sarcomatous change. The resemblance of these characters to those of human mammary fibro adenomas is obvious and the experimental results afford evidence that the connective tissue component of these growths has genuine neoplastic properties and is not merely a stroma to the epithelium.

It would be of great interest to carry out similar studies with teratomas and embryonic mixed tumours of the kidney occurring in animals and to ascertain whether their components could be segregated by transplantation. The gonadal teratomas of fowls and horses and the nephroblastomas of fowls rabbits, rats and pigs afford possible material for such research. Transplantation of carcino sarcomas of the dog's thyroid such as that described by Rudduck and me might enable separation of the epithelial and sarcomatous elements.

Occasionally a transplanted tumour induces in the host stroma metaplastic changes study of which throws light on some of the supposedly mixed tumours. Thus Foulds studied a transplantable carcinoma of a hen's oviduct in transplants of which bone and cartilage were prominent giving the tumours a mixed structure. These skeletal tissues however were formed by the host's connective tissue cells which were constrained to differentiate in this way by conditions

- Eber A and Kriegbaum A (1915) *Z Krebsforsch* 15 404
- Eisen M J (1940) *Amer J Cancer* 39 36
- Emge L A (1938) *Arch Path* 26 429
- FARDEAU, G (1931) *Les tumeurs spontanees chez le lapin* Versailles
- HELDMAN, W H (1932) *Neoplasms of Domesticated Animals* Philadelphia (A comprehensive monograph with many excellent figures)
- Ieldman W H (1931) *Amer J Cancer* 15 2044
- Flaks J (1932) *Z Krebsforsch* 37 504
- Foulds L (1932) *Imp Cancer Res Fund Sci Rep* p 21
- FOULDS L (1937) A transplantable carcinoma of a domestic fowl with a discussion of the histogenesis of mixed tumours *J Path Bact* 44 1 (A valuable study of metaplasia in the stroma of transplanted tumours)
- FOX, H (1923) *Disease in Captive Wild Mammals and Birds Incidence Description Comparison* London (Contains an important account of 94 tumours)
- Furth J and Kahn M C (1937) *Amer J Cancer* 31 276
- Gordon M and Smith G M (1938) *Amer J Cancer* 34 255 and 543
- Gorer P A (1938) *J Path Bact* 47 231
- Greene H S N (1942) *Cancer Res* 2 649
- Gross L (1932) *Z Krebsforsch* 37 562
- HAALAND M (1908) Contributions to the study of the development of sarcoma under experimental conditions *Imp Cancer Res Fund Sci Rep* p 175 (An admirable and beautifully illustrated account of transplanted tumours in mice and of the supposed sarcomatous change in the stroma of these tumours)
- HADDOW A, and BLAKE I (1933) Neoplasms in fish a report of six cases with a summary of the Literature *J Path Bact* 36 41
- HEIMAN, J (1934) The study of benign neoplasms of the rat's breast *Amer J Cancer*, 22 497 (An excellent paper beautifully illustrated)
- JOEST E and ERNESTI, S (1915) Untersuchungen uber spontane Geschwulste bei Vogeln *Z Krebsforsch* 15 1 (The best of the early accounts of avian tumours)
- Jungherr E and Wolf A (1939) *Amer J Cancer* 37 493
- Kahn M C and Furth J (1938) *Proc Soc Exp Biol* 38 485
- LUCKE, B (1934) A neoplastic disease of the kidney of the frog *Rana pipiens* *Amer J Cancer* 20 352 22 326 (A beautifully illustrated study of renal adenocarcinomas in frogs and a valuable review of other tumours in amphibia and reptilia)
- Lucke B (1937) *Arch Path* 23 292
- LUCKE, B (1942) Tumors of the nerve sheaths in fish of the snapper family *Arch Path* 34 133 (An admirable study with excellent illustrations)
- Maury A (1935) Les tumeurs chez le cobaye *Abst Amer J Cancer* 23 844
- MURRAY J A (1908) The zoological distribution of cancer *Imp Cancer Res Fund Sci Rep* p 41 (The most valuable early study of the pathology of animal tumours)
- MURRAY J A (1908) Spontaneous cancer in the mouse *Imp Cancer Res Fund Sci Rep* p 175 (An important early account of the subject)
- POLSON C J (1927) Tumours of the rabbit *J Path Bact* 30 603
- Ratcliffe H L (1932) *Amer J Path* 8 117
- RATCLIFFE H L (1933) Incidence and nature of tumors in captive wild animals and birds, *Amer J Cancer* 17 116 (A review of 32 years' findings at the Philadelphia Zoo)
- Ratcliffe H L (1935) *Amer J Cancer* 24 78
- Ratcliffe H L (1940) *Amer J Path* 16 237
- Robinson G H and Grauer R C (1932) *Amer J Cancer* 16 184
- RÜDDUCK H B and WILLIS, R A (1938) Malignant tumours in dogs *Amer J Cancer* 33 205 (A detailed account of nine selected tumours)
- Schlotthauer C F (1940) *J Amer Vet Med Assoc* 96 632
- Scott H H (1927) *J Path Bact* 30 61
- SLYE, M, HOLMES H F and WELLS H G (1917-1921) *J Cancer Res* Vols 2-6 (Several papers on the incidence of the various kinds of primary spontaneous tumours in a large stock of mice)
- Smith G M (1934) *Amer J Cancer* 22 838
- Steiner J, E Kluver H and Brunschwig A (1942) *Cancer Res* 2 704

fats, lipoids, the several vitamins, various acids and bases and inorganic salts but no conclusive or generally significant results have eventuated. Claims have also been made for the efficacy of extracts of spleen, placenta, embryonic and other tissues, or of feeding with these tissues but again the results are conflicting and undependable. While we know that the growth of some mammary and prostatic carcinomas is influenced by oestrogenic and related hormones there is no experimental evidence to show that insulin, thyroxine, parathormone, adrenaline, cortin or the pituitary hormones have any consistent influences on tumour growth in general.

Many of the claims for the therapeutic value of particular diets, hormones, vitamins, tissue extracts, bacterial products and other substances in the treatment of tumours have been urged with such lack of evidence and such unreasoning vehemence as to show the claimants to be either deliberately fraudulent or the victims of obsessions—and it is often difficult to distinguish between fraud and obsession. Subjection of any therapeutic claim to an adequate biological test on a large number of tumour-bearing animals under properly controlled conditions is a big undertaking, and not to be lightly embarked on unless the claim has a substantial basis.

Experimentalists and clinicians alike have harboured the hope of discovering some chemical agent which might selectively inhibit tumour growth or damage tumour cells. Lead, selenium, colchicine, isamine blue and other dyes have been amongst the substances which have raised false hopes of success. Clearly any substance presumed to possess cancer-inhibitory properties should be tested on a large scale on tumour-bearing animals before being applied to human sufferers. In the past much harm has been done by the indiscriminate and premature administration to human beings of supposed remedies which could and should have been tested first on animals. The excuse has usually been that the victims of hopeless cancers should not be denied the possible curative or palliative effects of new remedies pending their testing on animals—an excuse that has been responsible for a great deal of avoidable physical and mental suffering, to say nothing of a great deal of exploitation by quacks and cranks.

The most interesting researches on factors affecting tumour growth are those of Haddow and his co-workers on the inhibition of growth effected by the administration of carcinogenic agents. These are discussed in Chapter 8.

REFERENCES

- Antoine Liégeois and Verstraete (1934) *Bull Acad Roy Med Belg* 14 301
 Bashford E F and Murray J A (1924) *Imp Cancer Res Fund Sci Rep*
 BASHFORD E F MURRAY J A HALLAND M and BOWEN W H (1908) *General*
 results of propagation of malignant new growths. *Imp Cancer Res Fund Sci Rep* p 262
 (An important monographic account of tumour transplantation.)
 Belmonte V (1935) *Lancets Arch* 294 329
 Blumenthal F (1929) *Z Krebsforsch* 29 549
 Briggs R (1942) *Cancer Res* 2 309
 BULLOCK F D and CURTIS M R (1930) Spontaneous tumors of the rat. *J Cancer Res* 14 1 (A well illustrated monographic account of 521 tumours.)
 Burrows, H (1940) *J Path Bact* 51 385
 CRAMER W (1932) The Comparative study of cancer. *Cancer Rev* 7 241 (A valuable review.)
 Curtis, M R, Bullock F D and Dunning W F (1931) *Amer J Cancer* 15 67

CHAPTER 7

THE MODE OF ORIGIN OF TUMOURS

INTRODUCTION

THE MODE of origin of tumours, while clearly a matter of fundamental biological interest as well as of practical importance, has been strangely neglected or misunderstood by many modern pathologists. The most prevalent view has been that each tumour has a simple unicentric origin, arising at a single point in time, from a single small focus of cells, and enlarging only by multiplication of these cells and their descendants. This strict unicentric view is largely a legacy from Cohnheim's hypothesis of embryonic rests, which precluded the possibility of progressive cancerous change in neighbouring adult tissues. Although Cohnheim's hypothesis of the origin of tumours from superfluous embryonic cells has been abandoned by most modern pathologists, his concept of restricted unicentric origin and purely intrinsic growth has largely persisted. The prevalence of this view may be gauged from the following citations from well known works on tumour pathology.

Mallory (1923) insisted that 'Tumors grow entirely by multiplication of their own cells, not by transformation of normal cells into tumor cells', and that attempts to trace gradations between normal and neoplastic tissues are "founded on incorrect observation, interpretation and deduction". According to McFarland (1924) 'It seems well to think of a tumor as beginning at a minute focus starting, as it were, from a single cell or group of cells, and increasing in size through multiplication of the particular elements concerned. There seems to be no ground for assuming continuous transformation of normal tissue into tumor—no successive beginnings'. Kettle (1925) said, "It is generally held that tumours arise from one cell or group of cells, and not as the result of a change affecting a comparatively large area. Whatever may be the size of the tumour, all its cells are the direct descendants of the mother cells or cells. Ewing (1940), after briefly discussing the possibility that tumours may develop by progressive neoplastic change in a field of tissue, concluded 'yet these instances of lateral extension of tumor processes, if they eventually stand the test of criticism, are rare, and it should be emphasized that the great majority of tumor cells are isolated in origin and throughout their history'".

This chapter is to show that the strict unicentric view is false and that tumours arise from small or large fields of tissue and enlarge not only by cellular proliferation but also by progressive neoplastic conversion of tissue within those fields. Careful microscopic study of early tumours of many kinds affords clear evidence of such progressive change, with plain transitions from normal to neoplastic tissue. In many cases the extent of the potentially neoplastic field is much greater than the small size of the initially appearing tumour would suggest a point of great surgical importance.

The modes of origin of tumours of the various classes will be discussed and

- STICKER, A (1902) Ueber den Krebs der Thiere *Arch klin Chir* 65 616 and 1023 (A tabular outline of many tumours in various species of animals)
- TAKAHASHI K (1929) Studie über die Fischgeschwülste *Z Krebsforsch* 29 1 (A full account of many personally studied fish tumours with good illustrations)
- Twort, C C and Twort J M (1932) *J Path Bact* 35 976
- Voegtlin C (1937) *Physiol Rev* 17 92
- Wagner A (1938) *Z Krebsforsch* 48 40
- Warren S and Gates O (1936) *Amer J Cancer* 27 485
- White P B (1921) *J Path Bact* 24 138
- Wibeau E (1933) *Z Krebsforsch* 39 66
- WILLIS R A (1934) *The Spread of Tumours in the Human Body* London (Chapter 13 describes the experimental study of tumour metastasis)
- WOGIOM W H (1929) Immunity to transplantable tumours *Cancer Rev* 4 129 (An important review)
- Wright A W, Clinck G H and Wolfe J M (1940) *Amer J Path* 16 817

of these zones is nearing exhaustion. The structure of the transition zones in these specimens, as also of others described in my papers cited is quite unlike the familiar picture of previously normal epidermis suffering invasive replacement by an advancing tumour and no ingenious explanations, such as MacCallum's "secondary healing together" will suffice to make the supposition of a simple unifocal origin plausible.



FIG 3—Vertical section of squamous-cell carcinoma of dorsum of wrist of a woman of 75 years who had multiple keratoses of hands and face. XX = crater left by detachment of horny mass. Y = zone of transition from hyperplastic to neoplastic epithelium. C = deeply penetrating cancerous downgrowths. ($\times 4$)



FIG 4—Vertical section of squamous-cell carcinoma of neck of man aged 70. XX = crateriform lip of growth. EE = marginal epidermis like downgrowths of tumour. CC = active poorly differentiated carcinoma sharply delimited from E at the arrows. DD = thick layer of altered dermal elastic tissue. ($\times 6$)

As my previous papers showed, during the early stages of cancerous transformation of a field of prepared epidermis the structure observed may be further complicated by—(a) invasive invagination of the epidermis as it undergoes

illustrated in Part II of this work. The following paragraphs necessarily partly traverse the same ground, but with stress on the general aspects of the subject

FIELDS OF ORIGIN OF EPITHELIAL TUMOURS

(1) The epidermis

The sequence of changes taking place in skin destined to give origin to tumours is best followed in experimental material which can be properly controlled and studied at all stages as in the experiments of Deelman Orr Brunshwig and Tschetter and Glucksmann. However the pre cancerous and early cancerous changes observed by experimentalists, described in Chapter 4 find their close counterparts in human pathology. The changes seen in pre cancerous lesions of the skin such as keratoses X ray dermatitis, arsenical dermatitis and chronic ulcerative lesions and the transitions from these to carcinoma, parallel those seen in the genesis of experimental growths of the epidermis.

Elsewhere (1944 and 1945) I have depicted the structure of early squamous-cell carcinomas of the skin and lip, confirming the much earlier conclusions of Lohmer (1900) that these do not have a simple unifocal uni temporal origin and purely

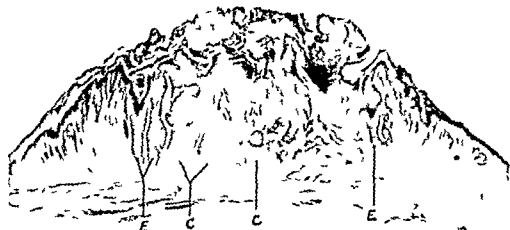


FIG. 2.—Vertical section of squamous-cell carcinoma of dorsum of hand of a tar worker aged 56
EE = downgrowths with perfect epidermal structure CC = atypical downgrowths. ($\times 7\frac{1}{2}$)

intrinsic proliferative growth. Figs 2 and 3 depict examples of such tumours which show—(a) gradual hyperplastic thickening of the surrounding epidermis as it approaches the growth (b) gentle transition from the hyperplastic to the neoplastic epithelium making it impossible to decide just where the one ends and the other begins and (c) retention by the cancerous epithelium of the general architecture of the epidermis but with extravagant papillation keratinization and some downward invasion of the dermis. The tumours display plain evidence of a progressive hyperplastic neoplastic change still taking place, in a centrifugal direction over fields of epidermis greater in extent than the present sizes of the growths i.e. at least 1.5 centimetres in diameter. Probably the actual size of the potentially cancerous field is much greater than this since there are wide zones of epidermal hyperplasia around the growths and there is no reason to suppose that we have chanced to examine the tumours just when the neoplastic potentiality

not one cancerous focus, but of several simultaneous foci, in a field of abnormal epidermis, (c) the appearance in the deeper invading parts of the tumour of more anaplastic downgrowths, clearly indicative of augmented rate of growth and invasive characters (Fig 5), and (d) the invasive replacement of the less active neoplastic epidermis by the more anaplastic component (Fig 4)

Of course it is not denied that an established tumour grows in bulk by cell proliferation in excess of that of the normal epidermis. What is to be insisted on, however is that a skin cancer in its early formative stage arises more by a general transformation of pre existing epidermis than by cellular multiplication and that only after the formative field has all suffered neoplastic change does the tumour grow solely by multiplication. The two processes, neoplastic transformation and proliferation, overlap, the former predominating during the early genesis of the tumour, the latter often being initially negligible but gradually taking an increasing, and finally exclusive, part in the growth of the tumour

While solitary localized epidermoid growths of the skin often have a field of origin demonstrably of at least 1 or 2 centimetres in diameter, in the case of multiple growths or of certain extensive superficial carcinomas the potentially neoplastic field is much greater than this. Thus in cases of multiple squamous-celled growths of the face and neck seen in fair-skinned people with widespread keratoses due to long exposure to light from outdoor occupations the whole of the epidermis of exposed areas is ready to become cancerous and the multiple tumours which actually develop merely denote the foci of maximal cancer potential in these areas. The extreme instance of this is seen in the rare disease xeroderma pigmentosum in which there is an inherited predisposition of the epidermis to neoplasia, and at an early age the patients develop numerous carcinomas of any areas of skin exposed to light. The inadequacy of the unicentric view in such cases is obvious, the cells of the entire epidermis in the susceptible areas are in an unstable pre cancerous state and many of them undergo cancerous transformation *in situ*.

So also it is clear that many skin cancers arising in association with scars or chronic ulcers or sinuses are not of simple unifocal origin but exhibit progressive cancerous change over more or less extensive sometimes multiple, areas of the epithelium clothing the scar or surrounding the ulcer (Figs 6, 7 and 8, and Willis, 1945)

Bowen's so called "pre cancerous dermatosis" is rather a form of widespread multifocal or diffuse cancerous transformation of epidermal cells *in situ* (Chapter 14). Paget's disease is probably of similar nature (Chapter 13). Vulval leucoplakia also, in some cases, is already a form of widespread intra epidermal carcinoma even before the appearance of the multiple areas of obvious growth which often supervene (Chapter 32). As long ago as 1897, Hauser carefully described a case of recurrent carcinoma of the vulva clearly arising progressively and in a wide spread manner in the diseased epidermis. Squamous cell carcinoma arising in the skin of a cystic teratoma is sometimes demonstrably widespread in origin (Willis, 1937 and Case IV, Chapter 61).

The frequently multicentric or diffuse mode of origin of basal cell growths of the skin must be apparent to anyone who studies these tumours at all closely



FIG. 5.—Vertical section of one half of a squamous-cell carcinoma of the pinna of a man of 57 years. X = invagination lip at margin of growth. FE = surface zone of epidermis-like growth. CC = more active carcinoma. PP = cartilage of ear. (16)

neoplastic change forming a characteristic invagination lip or circular rampart bounding an enlarging cancerous crater (Figs 3 and 5) (b) the appearance of,

(Lohmer, 1900, Molesworth, 1927, Willis, 1945, and Figs 9, 10 and 11) Of the superficially spreading type of rodent carcinoma Molesworth said, "the main tumour mass is being reinforced continuously by exactly similar cells produced



FIG 8—Extensive superficial epidermoid carcinoma of a deep sinus of the buttock in a woman of 28 years (*Case 1 Chapter 14*) ($\times 8$)

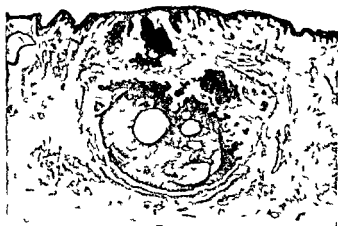
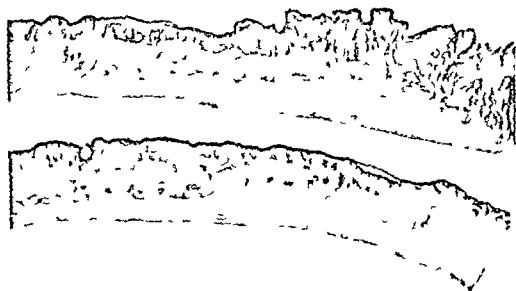


FIG 9—Small basal-cell carcinoma of the cubital fossa of a woman of 55 years who had also had multiple similar growths on the face neck and back. The structure points to simultaneous origin of the tumour from the interpapillary processes of the epidermis and a group of sweat glands and their ducts ($\times 12$)

not by reproduction from its own cells, but from those of neighbouring epithelium" Early specimens of the flat plaque like superficial basal cell carcinomas often



FIGS 6 and 7—Cancerous varicose ulcer from a woman aged 64. Fig. 6 is a general view following amputation—the transverse cleft is the site of removal of tissue for preliminary sections. Serial horizontal sections of the entire growth at planes 1 centimetre apart were prepared. Parts of two of these, in the marginal region of the growth, are shown in Fig. 7 (c.f.).

a large part of the body, many independent microscopic foci of growth may be found in skin not affected by visible growths (Fig 11)

That cutaneous melanomas arise by a progressive neoplastic change from considerable fields of epidermal cells is clear from Dawson's classical studies. Describing the early genesis of malignant change in pigmented moles, he said, "Similar changes occurred throughout the whole surface extent of the epithelium involved both in the rete processes and the intervening epithelium" Under the heading "Multicentric origin of the cutaneous melanomata", Dawson also said,

In the study of the advancing margins of many of the malignant melanomata, especially those which showed zones of pigmentation fading off into the normal skin numerous appearances were observed which pointed definitely to the presence of multiple and isolated points of origin of the early malignant change in the surface epithelium of rete epithelial processes. Not merely at the immediate advancing zone did the tumour growth appear to be increased by the early change taking place in the cells as it were *in situ* in their epithelial connexion but—in the large sections where the epithelium was followed serially over a large area adjoining the actual tumour—numerous isolated groups of intra epidermal cells could be found undergoing a malignant transformation. The truth of Dawson's conclusions is fully attested by his many beautifully depicted specimens and can be confirmed by any unbiased student of a few early growths of this kind

(2) Epithelial tumours of mucous membranes

Early carcinomas of the lip or tongue frequently show gentle transition from hyperplastic to neoplastic epithelium similar to that seen in tumours of the epidermis. Further, a carcinoma of the lip sometimes shows clear structural evidence that it has arisen partly from the epidermis and partly from the mucosal epithelium, the downgrowths of the epidermal and mucosal halves of the tumour differing in the same respects as their parent epithelia (Fig 12). In early lingual



FIG 12—Sagittal section of carcinoma of lip from a man of 41 years. The downgrowths of the half of the tumour continuous with epidermis (X) are more pointed and more cornuted than those of the half continuous with mucosal epithelium (Y). Also a distinct stratum granulosum was present in the former but not in the latter. ($\times 10$)

carcinoma there is often absence of demarcation between hyperplastic and cancerous epithelium, and the latter forms downgrowths from an intact surface layer over a considerable area of mucosa (Fig 13). Even some recurrent

show unmistakably their multifocal origin from many or all of the interpapillary epithelial processes in the affected area. Early specimens of the more bulky subepidermal basal cell growths often show evidence of their multifocal origin

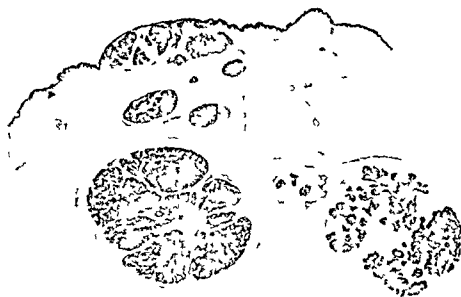


FIG. 10—Subepidermal basal-cell carcinoma of leg of a woman of 48 years. Structure plainly shows simultaneous origin from at least two groups of sweat glands and their ducts ($\times 8$)



FIG. 11—Panoramic view of a piece of skin from a man about 55 years old who had numerous superficial basal-cell carcinomas on the face, chest, back and elbows. The sections show multicentric and diffuse origin from the epidermis ($\times 50$)

from several groups of sweat glands and ducts or from several hair follicles and sheaths or from both (Figs 9 and 10). At the margins of well-established growths it is not unusual to find small satellite foci separate from the main mass. In those not infrequent cases of very numerous basal-cell tumours occurring over

the disease, there is a gradual extension of the area of origin by the progressive transformation of normal into neoplastic alveoli. The extent to which the lateral growth proceeds by this method is difficult to determine. In some cases there is a very wide superficial tumor involving 10 to 15 cm. of the mucosa, a form strongly suggesting a gradual inclusion of normal areas of mucosa." Tsunoda described a case of early gastric carcinoma with three separate areas showing transition from normal to cancerous epithelium. Konjetzny's opinion that gastric carcinoma usually arises in a multicentric or diffuse manner is convincingly supported by many excellent microphotographs (see also Chapter 21).



FIG. 14—Early recurrent carcinoma of tongue following radium treatment in an elderly woman showing an extensive field of similarly affected epithelium ($\times 10$)

From my own studies, I am satisfied that the foregoing views are correct, and that gastric or intestinal carcinoma often arises, not from a single minute focus but progressively over a field of prepared mucous membrane of small or great area. In cases of multiple polyposis of the colon with supervening multiple carcinoma, the potentially cancerous field is the mucosa of the entire large intestine and microscopic study will reveal many minute neoplastic foci unsuspected on naked eye examination.

Extensive diffuse carcinomas of hollow viscera, such as "leather bottle" carcinomas of the stomach and comparable growths of the biliary tract, are difficult to explain as the product of spread from a single original focus. Granting that these tumours are of a widely and diffusely infiltrating type, yet the walls of the viscus are often so uniformly affected over such extensive areas, sometimes the entire stomach or the entire extra hepatic biliary tract (Willis, 1942) that it is impossible to guess even approximately where the growth may have started first. It is much more plausible to assume that it arose, simultaneously or successively, over a large area or several areas of the mucous membrane. This supposition is supported by the occasional discovery of multiple separate areas of diffusely infiltrating carcinoma in these organs. Under the appropriate title 'carcinoma *in situ*', Mallory has described extensive superficial pre-invasive gastric carcinomas although he speaks of 'replacement' of normal by malignant cells and does not affirm a widespread origin, the latter seems to me to be the obvious interpretation.

The linings of ovarian cysts display striking comparable examples of the simultaneous multicentric or diffuse origin of papillary growths from a predisposed epithelium. All pathologists are familiar with specimens of these tumours in which similar papillary growths have sprung from the linings of many separate loculi and often from those of bilateral tumours. Even in a unilocular cyst

carcinomas of the tongue show clear evidence of origin *de novo* from a more or less extensive field of epithelium (Fig 14)

Although internal mucous membranes are less accessible for the study of the early genesis of tumours, there is ample evidence that this follows stages analogous to those already described. Early tumours of the stomach intestine, urinary tract or uterus sometimes clearly show neoplastic transformation still in progress and especially in cases with numerous multiple growths, as in papillomatosis of the large intestine, all stages in the development of the neoplasms from the mucosal epithelium can be traced



FIG 13—Vertical section of early carcinoma of tongue from a man of 69 years ($\times 7\frac{1}{2}$)

Long ago Hauser and Verse fully described early carcinomas of the stomach and intestine which clearly showed origin from many or all of the glands in considerable areas of the mucous membrane and marginal extension of the cancerous change still in progress. Thus Hauser while fully recognizing difficulties of interpretation caused by secondary cancerous infiltration of the mucous membrane described and depicted appearances which afforded irrefutable proof that in the earliest stages of the development of cancer a primary cancerous change of the glands of the mucous membrane in their entirety without their disintegration can be observed. Of gastric carcinoma Kaufmann said 'It is certain that multicentric development is frequent sometimes indeed from almost all the glands in the entire stomach wall. According to Ewing during the formation of the original focus and to a variable extent thereafter normal glands continue to be transformed into neoplastic structures. This lateral extension is more pronounced in the colon than in the stomach'. Of intestinal carcinoma Ewing concluded 'In the early stages of most cases, and in some throughout

Benign mammary tumours, as well as malignant ones, often display clear indications of multicentric origin, and additive as well as proliferative growth. In 1923 Cheatele first conclusively demonstrated that fibro-adenomas may be accompanied by satellite foci of growth and may enlarge by incorporation of these. Nicholson confirmed this. "The surrounding mammary lobules undergo the same minute changes that have already taken place within the body of the tumour, and are absorbed or incorporated into its substance." These conclusions can be verified by anyone who will take the trouble to examine microscopically the bed of mammary tissue in which a young growing fibro adenoma lies. This usually contains multiple fibro adenomatous foci derived from hyperplastic mammary lobules and there is often plain evidence of the addition of these to the main mass. It is largely this appositional form of growth which gives many fibro adenomas a lobulated shape, they are lobulated because they are of progressive conglomerate origin. Duct papillomas of the breast also are frequently multiple sometimes very numerous, and occasionally quite diffuse. Cheatele (1921, Fig 208) depicted a breast with over 70 little intra duct papillomas, as well as three separate areas of carcinoma, and Cheatele and Cutler showed that papillomatous change may affect the whole extent of a single main duct and all its tributaries a condition which they aptly likened to multiple papilloma tosis of the colon.

Multifocal neoplastic change of different types may be present in a breast. As Cheatele and Cutler said, "A breast which attracts clinical attention to one type of lesion is often a field in which other types of hyperplasia or neoplasia may be present and are likely to be present, the existence of which can be detected by the microscope." Full endorsement of this statement will be found in Chapter 13.

(b) *The prostate*

There is no doubt that carcinoma of the prostate resembles that of the breast in frequently supervening on cystic hyperplasia and in frequently being multifocal or diffuse in origin. Early cancerous change, not infrequently discovered by routine microscopic examination of surgically removed enlarged prostates, is often clearly of multiple patchy distribution. I have examined a prostate which, though scarcely abnormal in either size or consistency, was found microscopically to have undergone almost universal cancerous change *in situ*.

(c) *The liver*

Carcinoma especially liver cell carcinoma, arising in cirrhotic livers is frequently multiple the multiple growths sometimes being very numerous (see Chapter 24). Early tumours supervening on haemochromatosis often have a distinct lobular pattern strongly suggesting that many separate liver lobules have undergone progressive cancerous change *in situ* (Willis, 1941).

(d) *The pancreas*

In 1936 I described an example of almost complete cancerous replacement of the pancreas without enlargement of the organ and with retention of normal lobular pattern, pointing clearly to the diffuse origin of the growth. Lohmer

papillomatous changes are often so extensive and so uniform as to preclude their origin from a single focus and indeed microscopically all transitions between quiescent cyst epithelium and papillomatous masses can be traced. In pathological cysts of other organs also papillary growths may arise in a clearly multicentric or diffuse manner, as in my case of papillary carcinoma of congenital cysts in the liver (Willis, 1943)

(3) Glandular organs

(a) The breast

That mammary tumours often arise simultaneously or successively from extensive tracts of breast tissue is clear from the work of Cheate (1921) Nicholson (1921) Cheate and Cutler (1931) and Muir (1941). To Cheate belongs the credit of first demonstrating this conclusively in sections of whole breasts and for insisting that the primary cancer process transforming epithelial into malignant cells may commonly operate on extensive duct surfaces. Having been established at one part of a duct it may affect other parts of it or other ducts. Nicholson endorsing Cheate's conclusions said 'I have insisted for years that hyperplasia passes insensibly into carcinoma and that this gradual change can nowhere be better studied than in the breast and that tumour formation is here multicentric, or rather omnicentric'. Muir expresses the same conclusions as follows: 'Malignancy is often not only of multicentric origin but can be seen to occur gradually and to affect groups of cells in a diffuse fashion all stages of the process being traceable, the neoplastic change is regional rather than focal'.

I cannot understand how anyone who has examined cancerous breasts carefully could fail to endorse these conclusions. In Chapter 13 examples from my experience of multiple or diffuse origin of mammary carcinoma are described. Sometimes multifocal origin is obvious enough even to the naked eye: on sectioning an amputated breast into serial slabs two or more clearly separate growths may be found instead of the expected one. Rarely even the clinician is aware of the presence of two growths in the one breast or of simultaneous primary growths in both breasts. More often multicentric origin is less obvious and is found only by microscopic study of various parts of the breast. Especially in cases of carcinoma supervening on cystic hyperplasia in addition to the main tumour there are often present in other parts of the organ inconspicuous papillomatous or carcinomatous foci only to be discovered by deliberate microscopic search. The ideal conduct of such search is by whole sections of the breast as described by Cheate, but much may be learnt from multiple small sections from selected suspicious areas.

Diffuse origin of carcinoma in part or the whole of a breast is not rare. Like Cheate and Muir I have studied specimens of universally indurated 'shotty' breasts removed by the surgeon because of persistent supposed 'chronic mastitis' and in which there was no clinical or naked eye evidence of localized tumefaction yet microscopic study has shown the entire breast to be cancerous and the disease clearly to have arisen not by spread from any particular initial focus but by simultaneous or rapidly successive neoplastic change of much or all of the mammary epithelium *in situ*. Cases of bilateral carcinoma of this type are not unknown and I have several specimens showing simultaneous diffuse carcinoma of all pairs of mammae in dogs.

is also good evidence that simultaneous or successive multifocal neoplastic change occurs in these tissues (see Chapters 49 and 50)

FIELDS OF ORIGIN OF NEUROGLIAL TUMOURS

Most gliomas show absence of marginal demarcation from surrounding nervous tissue and many of them are quite diffuse. The surgeon often finds it impossible to determine even approximately the limits of the tumour, and its mingling with the normal tissues may be so gentle and so extensive that even microscopically its limits may be quite indefinite. In extreme cases the diffuse gliomatoses much or the whole of a cerebral hemisphere or even a large part of both hemispheres may be diffusely affected, the tissues showing only slight general enlargement with blurring of normal markings but no localized tumour mass. While the infiltrative powers of gliomas are admitted, there is little doubt that these highly diffuse tumours are due to extensive origin rather than to extensive spread. Scherer expresses this view as follows: all cerebral astrocytomas should be considered as primary diffuse neoplastic proliferations of the neuroglia of considerable areas of the brain not as primarily circumscribed nodules with subsequent diffuse spread. Study of my own material convinces me that this view is correct. That astrocytic tumours are sometimes multiple and that separate growths of both diffuse and more localized types may coexist affords additional evidence of origin from fields of neuroglial tissue.

MULTIPLE OR FIELD ORIGIN OF TUMOURS RELATED TO DEVELOPMENTAL DISTURBANCES

Many of those tumours which owe their origin to disturbances of early development show multiple and occasionally diffuse origin. This applies to neuroblastomas, retinoblastomas, nephroblastomas and teratomas. It applies also to neurofibromas, angiomas and multiple exostoses and chondromas, though some of these are not true tumours. Multiplicity of any of the foregoing must clearly depend on influences affecting many parts of the developing tissues simultaneously. Sometimes the tumour-evoking effect of these influences may be universal throughout the entire field of similar tissue, e.g. the foetus described by Potter and Parrish showed generalized neuroblastomatous change in all of the sympathetic ganglia, both adrenal glands and in some of the other viscera.

IMPLICATION OF FIELD ORIGIN REGARDING THE CAUSATION OF TUMOURS

Some of those who have correctly observed that tumours enlarge by spreading neoplastic transformation of surrounding tissue have supposed this to be due to some carcinogenic influence exerted by the tumour cells on their normal neighbours. Thus Welsh speaks of 'the passage of a malignant influence from cancer cells to adjacent non-cancerous epithelial cells, whereby the latter are induced to become cancerous *in situ*'. Molesworth speaking of the progressive genesis of basal cell carcinomas of the skin said, 'It almost appears as if the fever of proliferation were contagious' and again 'the tumour spreads by stimulation of the neighbouring epithelium into activity identical with that which produced the original tumour mass by infecting it as it were with the fever which drove the original

long ago described pancreatic carcinoma in which the tumour enlarged not only by intrinsic growth and replacement of surrounding tissue, but also by participation in the epithelial multiplication of fresh glandular tissue marginal to the tumour

(e) *The salivary glands*

Chapter 17 contains a description of the evidence which shows conclusively that the pleomorphic (so-called mixed) tumours of the salivary glands often take origin progressively from the surrounding glandular tissue. Direct transformation of salivary acini into tumour can be seen and this change may be demonstrable at multiple widely separate places around or within the tumours

(f) *The testis*

That seminomas may arise from extensive or multiple areas of seminal tubules is shown by the sometimes demonstrable multiplicity of these growths by their extensive replacement of testicular tissue without enlargement of the organ and by microscopic appearances pointing to progressive genesis features which are particularly well seen in early seminomas in dogs (see Chapter 33)

FIELDS OF ORIGIN OF NON EPITHELIAL MESODERMAL TUMOURS

The extent of the fields of origin of leiomyomas, lipomas, meningiomas and many other non-epithelial growths is still uncertain. In many cases it is clearly small but it is almost certainly not unicellular and perhaps not even microscopic in size. Thus in the wall of the uterus the muscle fibres lie, not separately or chaotically but in compact groups and bundles and it seems likely that anatomical and functional units such as these would also be the pathological units and therefore the birthplaces of myomas. Careful study of serial sections of parts of the myometrium in uteri containing many small myomas supports this conception. The earliest recognizable myomatous foci are non-encapsulated whorled or fasciculated groups of fibres distinguishable only with care from normal tissue and even visible myomatous nodules may show at parts of their peripheries absence of clear demarcation between normal and myomatous tissue. However there is little doubt that myomas enlarge chiefly by their own intrinsic proliferation, and that additive growth is largely confined to quite young tumours.

Lipomas also may well arise not from single adipose cells but from lobules or groups of lobules of fatty tissue. Their subsequent growth may well be largely or entirely proliferative and intrinsic. However lipomas do occur which are not everywhere well demarcated from the surrounding tissue and the possibility must be conceded that these may have enlarged by incorporation of neighbouring lobules of adipose tissue.

While many meningiomas by the time they are examined are large well circumscribed growths incapable of affording information as to their mode of origin the occasional extensive plaque like growths suggest an extensive origin from a considerable area of meningeal tissue.

Neoplasms of the haemopoietic tissues the leukaemias lymphosarcomatosis Hodgkin's disease and multiple myelomatosis have long been regarded by most pathologists as system diseases and although metastatic dissemination certainly plays an important part in the wide distribution of the lesions there

elevated part of the sessile growth is its centre, because here the tumour is oldest and excessive proliferation has been in progress longest, the bulk of the epithelium gets progressively less towards the periphery, because of the progressively less length of time during which neoplastic proliferation has been present

Should a papilloma have arisen in a relatively small field of epithelium and have thereafter grown considerably by proliferation, it will be of the pedunculated form shown in Fig 15D with a narrow base corresponding approximately in extent with the initial area of origin and a prominently projecting mass of more or less complexly branched structure. The supervention of malignant change in such a tumour may at first bring about little change in its gross form, but later invasive growth is likely to enlarge the pedicle and occasion irregular ulceration

Needless to say in many advanced malignant tumours of surfaces proliferative and invasive growth predominates and soon completely masks all evidence there may originally have been of marginal additive growth. Nevertheless, such evidence

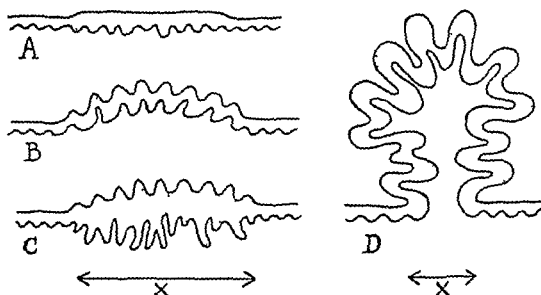


FIG 15—The shape of a tumour as determined by its mode of origin. A = epithelial tumour *in situ*. B = sessile papilloma. C = sessile papillary carcinoma. D = pedunculated papilloma of restricted field of origin. X = extent of origin.

is not restricted to very early growths but may often be found if looked for in well-established tumours in which neoplastic change still in progress may continue to play a part in determining the form of tumour margins

In solid organs also the mode of genesis of tumours may determine their shapes. The most striking example, already mentioned is afforded by the mammary fibro adenomas the lobulated form of which is clearly due in many cases to coalescence of multiple originally separate tumour lobules or to the addition of new tumour lobules at the margins of the main mass. Mammary carcinomas also may show irregularly lobulated or branched outlines due to multifocal or diffuse origin in a particular territory of tissue. The most notable instances of this are those tumours which as described by Cheate and Cutler, have arisen or are still arising from the entire extent of a main duct and all its peripheral branches

area of epithelium to proliferate' It has been suggested that this transferred contagion' might be a virus or perhaps some special carcinogenic enzyme

However, in order to account for marginal additive growth there is no need to assume the existence of any mysterious cancer inducing influence or contagion passed from tumour cells to adjacent healthy ones As the foregoing account of diffuse and multifocal modes of origin shows, most kinds of tumours arise in more or less extensive fields of prepared tissue The first spot to display visible neoplasia is only the region where neoplastic potential (compounded of intrinsic susceptibility of tissue and the incidence of all past extrinsic carcinogenic stimuli applied to it) was greatest Extending outwards from this maximal point there is a field of diminishing potential covering a small or large area, and the tissue just marginal to the initial focus of neoplasia which is only slightly less prone to neoplastic change than the focal tissue itself soon follows it into active growth Marginal addition is thus not an inductive effect of cancerous on normal cells but merely the progressive response of the tissue field to which effective carcinogenic stimuli have at some time in the past been applied a response the timing and distribution of which are determined by the intensity and distribution of those stimuli

In the light of experimental and occupational carcinogenesis the sequences observed are indeed what might have been expected Carcinogenic agents are applied not to single cells or minute groups of cells but to many cells in considerable areas of tissue All of the cells in the area are acted on similarly though of course not equally The neoplastic change which is the end product of the response will usually take place not simultaneously throughout the tissue destined to undergo it but in a particular sequence dependent on the quantitative gradients of the effective original stimulation That this concept accords with what is actually observed to take place in many tumours is strong evidence that they are due to external carcinogenic stimuli comparable with those used experimentally Embryonic rests malignant influences or contagions in the tissues are superfluous assumptions

THE INFLUENCE OF THE MODES OF ORIGIN ON THE GROSS FORMS OF TUMOURS

The extent of the field of origin and the relative importance of the two processes of neoplastic conversion and proliferation within that field are important factors in determining the shape of the resulting tumour Examples will make this clear

Suppose neoplastic change to occur in many or all of the cells of a surface epithelium *in situ* with little proliferative increase in the number of cells The tumour will then appear only as an area of altered epithelium with little increase in bulk and therefore little elevation above the general surface level Bowen's intra-epidermal carcinoma is such a tumour (Fig 15A) and analogous tumours in mucous membranes are the early non invasive carcinomas *in situ* of the alimentary tract described by Hauser Mallory and others

Now suppose considerable proliferative increase in bulk to accompany early progressive neoplastic change in a field of epithelium If the tumour is non invasive that is a benign papilloma it will assume the form shown in Fig 15B if invasive that in Fig 15C In Figs 15B and 15C the bulkiest and therefore most

tissue sometimes the whole breast, and since, as Cheate and Cutler correctly say, a breast which attracts clinical attention to one type of lesion is often a field in which other types of hyperplasia or neoplasia may be present and are likely to be present, clearly mammary cancers or any other persistent lesions deemed irreversible and potentially cancerous necessitate complete removal of the affected organ. This is not to deny that strictly localized early cancers of the breast may sometimes be successfully eradicated by local excision as suggested by Fitzwilliams. Nevertheless, local excision of mammary cancers in general even early ones is pathologically unsound, for there are many growths which, contrary to the prevalent assumption on which Fitzwilliams bases his conservative method do not start as a local change, perhaps one cell taking upon itself the characteristics and habits of malignancy. For patients curable by local excision simple mastectomy will also be curative. For the much more numerous patients with tumours which seem to the clinician to be localized but in whom other parts of the breast contain undetected potential or actual cancerous changes simple mastectomy will sometimes be curative when local excision would certainly fail.

HYPERPLASIAS AS PRE NEOPLASTIC STATES

Amongst the commonest sites of tumour formation are those tissues in which pathological forms of hyperplasia are frequently seen—these include the breast, uterus, prostate, thyroid and other ductless glands, liver and skin. Moreover, in all of these situations transitions from hyperplasia to neoplasia are frequent. In the breast, fibro-adenomas are almost always situated in a bed of hyperplastic tissue, and persistent cystic hyperplasia is an important pre-cancerous state. In the uterus various kinds of abnormal endometrial hyperplasia are frequent, and some of these pass insensibly into carcinoma. Carcinoma of the prostate frequently arises in an organ already the seat of benign enlargement. Most thyroid adenomas and carcinomas develop in glands already goitrous, and there is reason to believe that analogous hyperplastic strumas may precede the development of tumours of the pituitary gland, adrenal cortex and other endocrine tissues. The close relationship of hepatic adenomas and carcinomas to regenerative hyperplasia is well known. In the skin, epidermal hyperplasias evoked by various irritative and inflammatory lesions sometimes become cancerous—carcinoma may supervene in keratosis, chronic ulcerative lesions around the sinuses of osteomyelitis, in X-ray or radium burns and so on. In all of these cases it appears clear that the abnormal stimuli—regenerative or hormonal, which call forth hyperplastic proliferation in the tissues—proliferation which is at first reversible should the stimuli cease to act—may should they persist eventually evoke progressive neoplasia as well. To the student of tumour causation, then, the nature and causes of hyperplasias are of fundamental interest.

The obvious relationship of hyperplasia and neoplasia in certain cases however must not be allowed to mislead us. There are legion hyperplasias which never end in tumour formation, and there are many tumours which develop without any recognizable previous hyperplasia. Clearly then the causation of a tumour involves more than the mere persistence of hyperplasia evoking stimuli. The specific nature of the stimulus is all important, for example, on the experimental side both carbon tetrachloride and aminoazotoluene cause liver damage followed

the tumour accordingly being of an irregularly pyramidal form with apex towards the nipple

THE SURGICAL IMPORTANCE OF FIELDS OF ORIGIN

As long ago as 1865 Karl Thiersch taught that recurrence of an epithelial tumour following surgical removal was not always due to incomplete removal of tumour tissue but was sometimes due to fresh cancerous change in the predisposed epithelium of the region. This view though based on good objective evidence was unfortunately superseded by the teachings of Cohnheim and Ribbert, whose unicentric views on tumour genesis though speculative and erroneous have strongly influenced pathological thought ever since. Hauser, Lohmer and others indeed strongly opposed Ribbert's sequestration hypothesis and advanced clear evidence for the progressive field origin of epidermal and other tumours and for the correctness of Thiersch's teaching regarding recurrence. However, in spite of the conclusive evidence presented by these workers many surgeons and pathologists even to day continue to assume that tumours take origin from single small foci of tissue, and therefore that recurrence following excision is due to incomplete removal of tumour tissue. Exposure of the falsity of this assumption has been the main theme of the present chapter. Thiersch was right and Cohnheim and Ribbert were wrong, and the pathological basis of surgical practice must be clarified accordingly. The following instances will serve to show the great practical importance for the surgeon of correct views on the mode of origin of tumours.

Because many solitary localized carcinomas of the skin and lip take origin from relatively small fields of tissue they are successfully excised with no subsequent recurrence. But there are other cutaneous growths which, because of the extent of their fields of actual or potential origin carry much greater risks of recurrence. Such are the cancers arising in burn scars, vulval leucoplakia, chronic ulcers, radiation dermatitis and other chronic inflammatory lesions, Bowen's epidermal carcinoma *in situ* and the multiple squamous cell or basal cell growths in people with highly sensitive skins, the extreme instance being the inherited disease xeroderma pigmentosum. In all of these cases, the surgeon knows that the risks of recurrence following extirpation of established areas of growth are very great. He less frequently recognizes clearly that the recurrences are due not to incomplete removal of tumour tissue but to fresh cancerous change in similarly predisposed tissue. If, then, cancer appears in a burn scar or chronic ulcer the entire scarred or ulcerated area must be looked upon as a likely field of subsequent cancerous change and the proper surgery is not merely excision of the cancerous area, but extirpation of the entire prepared field—amputation if need be. So also vulval leucoplakia which has commenced to become cancerous necessitates radical vulvectomy. Mere local removal of an area of growth is almost certain to be followed by recurrence elsewhere. The surgeon of course recognizes his limitations in cases of multiple skin cancer with xeroderma pigmentosum or other highly sensitive skins, the only fully adequate surgery in such cases would be slaying.

Mammary surgery should take cognizance of the mode and extent of origin of mammary tumours. Since in many cases cancer of the breast arises not from a single minute focus but from a considerable field of predisposed mammary

CHAPTER 8

STRUCTURE AND GROWTH OF TUMOURS

THE STRUCTURE and growth of particular kinds of tumours are described in the special chapters of Part II. Certain general aspects of the subject however, require comment here. For further details and references, see Nicholson's *Tumour Studies* my 1934 work, and the papers of Foulds and Cowdry.

TUMOUR STRUCTURE AND FUNCTION

(1) The degree of organization of tumours

In Chapter 3 it has already been noted that most benign tumours show a high degree of differentiation and organization, and many malignant tumours incomplete differentiation or anaplasia but that some malignant tumours have a highly organized structure. This last point deserves emphatic repetition. The degree of differentiation and organization seen in many papillary carcinomas and adenocarcinomas approaches that of the normal tissues, and serial reconstructions of such tumours (references by Foulds) have shown that they have orderly patterns and grow in obedience to rules which, in part, resemble those which regulate the growth of normal tissues". With the statement of Reimann and Toennies,

Benign growths have an organization, while malignant ones do not", surely no competent pathologist will agree.

(2) Metaplasia in tumours

Tumour tissue probably never shows any peculiar metaplastic changes of which the parent normal tissue is incapable in non neoplastic lesions. Squamous metaplasia in glandular carcinomas of the uterus (Fig 16), bronchi, alimentary canal, breast, salivary glands or nasal cavity, has its parallel in similar metaplasia in inflammatory or hyperplastic states of these epithelia. The same applies to osseous or cartilaginous metaplasia, which is seen in reparative and inflammatory states of the mesenchymal soft tissues as well as in some of their tumours. However in certain situations tumours are by far the most frequent pathological lesions to disclose the dormant metaplastic potentialities of the parent tissues. Thus squamous metaplasia in the epithelia of the gall bladder, pancreas, gastrointestinal tract or breast is very rare save in carcinomatous tumours. So also although it has often been stated that squamous change commonly occurs in chronic bronchiectasis or bronchitis this is an error, except in carcinomas. Squamous metaplasia in human bronchial disease is rare. Mucus secreting carcinomas of the breast (Fig 17b) reveal a metaplastic potency of mammary epithelium which is rarely disclosed in any other lesion. Goblet cell metaplasia has occasionally occurred even in carcinomas of the skin (Nicholson 1923). The difficult question of the histogenesis of many of the ovarian tumours involves consideration of the metaplastic potencies of the ovarian tissues—potencies which but for the existence of the tumours we would hardly suspect.

by regenerative hyperplasia but tumour formation is rarely seen following the former and very frequently following the latter and on the clinical side while alcoholic cirrhosis seldom leads to hepatic tumours the cirrhosis of haemochromatosis quite frequently does so. Of importance also is individual susceptibility of a particular tissue to tumour formation for example the epidermis of a person with xeroderma pigmentosum or the intestinal mucosa of a person destined to develop familial polyposis is in an unstable state and is ready to become neoplastic on slight provocation. In such susceptible tissues it is probable that mild physical or chemical stimuli of diverse kinds insufficient to effect permanent changes in normal tissue suffice to evoke persistent hyperplasia and eventual neoplasia.

REFERENCES

- Brunschwig A and Tschotter D (1938) *Surg Gyn Obst* 67 715
- CHEATLE G L. *References* Chapter 13 (Classical studies of the extent of origin of breast tumours)
- Cohnheim J (1889) *Lectures on General Pathology* Vol II p 789 (translated by A B McKee) New Sydenham Society London
- Dawson J W (1925) *The Melanomata* *Lancet Med J* 32 509
- Dreiman H T. *References* Chapter 4
- Ewing J (1940) *Neoplastic Diseases* p 22 Philadelphia
- Fitzwilliams D C L (1940) *Brit Med J* ii 405
- Glucksman A (1945) *Cancer Res* 5 385
- HAUSER, G (1897) Beitrag zur Histogenese des Plattenepithelkrebses und zur Lehre vom regionalen Reiz. Thiersch's *Beitr path Anat* 22 597 (An excellent paper refuting Ribbert)
- Kaufmann E (1929) *Pathology* (translation by S P Reimann) Philadelphia
- Kettle E H (1925) *The Pathology of Tumours* p 7 London
- Konietzky G E (1938) *Der Mastenkrebs* Stuttgart
- LOHMEYER, H (1900) Ueber das Wachstum der Haut und Schleimhautcarcinome. *Beitr path Anat* 28 372 (An admirable well illustrated account refuting Ribbert and upholding origin from fields of epithelia)
- MacCallum W G (1942) *A Textbook of Pathology* p 1140 Philadelphia
- McFarland J (1924) *Surgical Pathology* p 212 Philadelphia
- Mallory F B (1923) *The Principles of Pathologic Histology* p 258 Philadelphia
- Mallory T B (1940) *Arch Path* 30 348
- Molesworth F H (1927) *Med J Austral* 1 878
- MILIR R (1941) The evolution of carcinoma of the mamma. *J Path Bact* 42 155
- Nicholson G W (1921) *Brit J Surg* 8 527
- Nicholson G W (1924) *Gyn & Hosp Rep* 74 81
- Orr J W (1938) *J Path Bact* 46 495
- Forster E I and Parrish J M (1947) *Amer J Path* 18 141
- Ribbert H (1895) *Lichens Arch* 141 153
- SCHIRER H J (1940) Cerebral astrocytomas and their derivatives. *Amer J Cancer* 40 159 (An admirable exposition of the field origin of gliomas)
- Thiersch cited by Hauer
- Tsunoda T (1910) *Z Krebsforsch* 9 436
- VERSE M A (1905) Ueber die Entstehung den Bau und das Wachstum der Polypen Adenome und Carcinome des Magendarmkanals. *Arbeit path Inst* Vol I Leipzig (A classical account)
- Verse M A (1905) *Verh Dtsch path Ges* p 95
- Welsh D A (1940) *Med J Austral* 1 287
- Willis R A (1936 1937 and 1943) *J Path Bact* 1936 42 703 1937 45 49 1943 55 432
- Willis R A (1941 and 1947) *Med J Austral* 1941 ii 666 1942 ii 340
- Willis R A (1944 and 1947) The mode of origin of tumours. *Cancer Res* 1944 4 670 1945 5 469 (These papers amplify the writer's views on the origin of carcinomas of the skin with many examples)

this is seldom so great as to deprive the tumours wholly of recognizable resemblance to their parent, and a general preservation of type is usually apparent

(4) Structural variations in a single tumour

It is of great importance to recognize that, not only do different tumours in one class show individual differences of structure, but that a single tumour may show a great variety of structure. Thus a cancer of the breast may contain

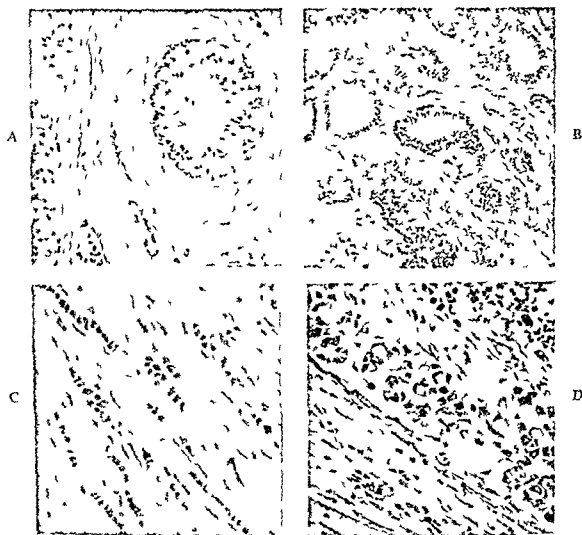


Fig 17—The range of structure in a carcinoma of the breast. A = intra duct carcinoma in large ducts ($\times 100$) B = in small ducts ($\times 100$) C = scirrhous spheroidal celled carcinoma ($\times 225$) D = signet ring celled carcinoma ($\times 225$)

areas of cribriform intra duct carcinoma areas of papillary growth areas of infiltrating adenocarcinoma and areas of polyhedral-cell carcinoma partly of medullary and partly of scirrhous type (Fig 17) A bronchial tumour may contain areas of adenocarcinoma mucoid carcinoma, squamous cell carcinoma and diffuse oat cell carcinoma. A thyroid tumour may display the whole gamut of possible structure, from perfectly differentiated thyroid vesicles, or

(3) Individuality in the structure of tumours

One of the most remarkable properties of tumours is the stability of individual characters which they show. Each tumour has its own peculiarities of structure and behaviour which it maintains largely unchanged even through a long and complicated metastatic career (Willis, 1934, Chapter 7). The same applies to transplantable animal tumours: repeated serial transplants maintain, with minor variations, the special characters of the parent tumours. "Each tumour has specific properties, tumours owning the same parent tissue have family resemblances but individual peculiarities. All these properties are permanent and hereditary" (Foulds). This remarkable stability of individual type shows more clearly than any other single fact that neoplasia consists in an irreversible change in the tumour cells themselves and not in any adventitious change in their environment.



FIG 16—Squamous metaplasia in endometrial adenocarcinoma ($\times 120$)

Minor variations of structure doubtless due to variations of available nutrient and other extrinsic factors, are seen in different parts of a tumour or in its metastases or transplants. Apart from mere degenerative changes these variations comprise increased or decreased structural differentiation as compared with the normal structure of the parent tumour. Increased structural differentiation is exemplified by occasional instances in which a metastasis of an anaplastic epidermoid carcinoma may show well keratinized squamous-cell areas, or a metastasis of a cellular poorly differentiated carcinoma of the thyroid may show some typical colloid filled thyroid vesicles. Decreased structural differentiation i.e. increased anaplasia is not unusual in metastatic growths. These often show greater mitotic activity than their parent primary tumour, especially in the liver (Willis 1932) with corresponding diminution of organized pattern. But

these features occur in some cellular carcinomas and teratomas. Even when a tumour has been correctly identified as epithelial, mistakes in diagnosis may be occasioned by mimicry of special appearances in the tumour tissue. Squamous cell or basal cell carcinoma may present pseudo glandular appearances (Fig 19), thyroid vesicles may be simulated by glandular spaces filled with eosinophil secretion in glandular tumours of other organs, and fatty or glycogenic change in the cells of a carcinoma may cause it to simulate the appearance of renal carcinoma (Fig 20).



FIG 18—Spindle-celled area of a lymph nodal metastasis of a squamous cell carcinoma of the tongue the fusiform tumour cells mingling diffusely with the fibroblastic stroma ($\times 82$)



FIG 19—Pseudo glandular appearance produced by desquamation and degeneration of the centres of the downgrowths of a squamous-cell carcinoma of the skin ($\times 70$)

(6) Secretory function in tumour cells

There is probably no glandular tissue endocrine or exocrine, the special secretion of which is not produced in some of its innocent or malignant tumours. Many examples of such secretory activities are referred to by Nicholson, Willis (1934) and Cowdry. The most familiar instance of an exocrine secretion in tumours is the mucus produced so plentifully in the 'colloid' or mucoid adenocarcinomas and less plentifully in the signet ring cell carcinomas and in the pleomorphic salivary tumours. The production of bile by carcinomas of the liver (references by Willis), and of digestive enzymes by carcinomas of the pancreas are also well known. Mammary fibro adenomas may lactate (Nicholson Fig 2 Geschickter and Lewis) and this applies also to transplanted adenomas in lactating rats (Grauer and Robinson).

cystic areas filled with colloid to diffuse masses of cells indistinguishable from sarcoma. This structural heterogeneity does not conflict with the principle of tumour individuality enunciated above, the range of structure displayed by a particular tumour is itself one of its peculiarities.

The frequently variegated structure of individual tumours shows both the arbitrary nature of histological sub-divisions of any single species of tumour and the pitfalls awaiting tumour graders. To set out, for example, to label all bronchial carcinomas either squamous celled, oat celled or adenocarcinoma is both futile and impossible. The entity is *bronchial carcinoma*, and all other prefixes or adjectives are merely descriptive of the possible variations of structure seen in tumours or in a tumour, of that species. Certainly in many tumours one or other variant predominates and it is legitimate to inquire whether predominance of particular variants has any bearing on prognosis. But certainly also, most such inquiries are vitiated from the outset because no exhaustive microscopical study of the tumours to ascertain their complete structural composition, has been or could be made. Hence, as already stressed in Chapter 3 attempts at precise numerical grading of tumours for prognostic purposes are wasted effort.

(5) Mimicry in tumours

The structural versatility of cancerous epithelium pointed out by many workers (e.g. Kettle, Cohn Willis 1932 and 1934, Tudhope and Chisholm, Cappell, Saphir and Vass, Brooks) is not sufficiently appreciated by most pathologists. Anaplasia, metaplasia, stromal reactions accompanying inflammatory changes, adaptation to the architecture of invaded tissues—all these factors operate to disguise the epithelial nature of many carcinomas and to simulate the structure of other kinds of tumours (Fig. 18). It is still a prevalent habit to dub any highly cellular diffuse tumour sarcoma, overlooking the obvious fact that any kind of tumour when sufficiently anaplastic and rapidly growing is diffusely and highly cellular. It is time too for pathologists to recognize that study of the fine relationships of stromal collagen or reticulin to the cells of anaplastic tumours of doubtful nature will not enable carcinomas, sarcomas and other tumours to be distinguished.

Some further specific warnings against possible histological misdiagnoses may be mentioned briefly here. A cellular tumour containing scattered brown pigment is not necessarily a melanoma; it may be a carcinoma or some other growth with admixed residues of former haemorrhages. A cellular tumour with vacuolated fat laden cells is not necessarily a liposarcoma; it may be a carcinoma with some fatty degeneration of its cells or with many macrophages laden with degeneration products. A highly vascular tumour with tumour cells lining blood filled spaces is not necessarily an angioblastic tumour; it may be an anaplastic vascular carcinoma or a vascular adenocarcinoma with haemorrhage into glandular spaces. A tumour composed of spindle-cells and multinucleated giant cells indiscriminately arranged is not necessarily a polymorphous-celled sarcoma; these features are common in parts of anaplastic carcinomas. A tumour containing large irregular multinucleated syncytial masses associated with extensive areas of haemorrhage is not necessarily a chorion-epithelioma.

nucleoli for many years, concluded (1936), "The nucleolus is much larger in proportion to the size of the nucleus in all malignant cells, regardless of the type or origin of the neoplasm, this difference being great enough to permit easy differentiation from all other cells in the hands of one experienced with fresh tissues" This conclusion is cited only as an example of the dangers of preoccupation with one small facet of a large problem To any pathologist aware of the absence of sharp distinctions between benign and malignant tumours, of the gradual nature of the neoplastic change, and of the close resemblance of some well differentiated malignant tumours to the corresponding normal tissues both in general architecture and cellular details, such a conclusion will of course appear absurd Cowdry and Paletta measured the sizes of the cells, nuclei and nucleoli, in many experimental and human epidermal carcinomas, and found that, while many malignant cells showed a high nucleocytoplasmic ratio and large nucleoli, no single cellular measurement made yielded results so characteristic of malignant cells as to differentiate them invariably from neighboring hyperplastic epidermal cells

Nuclear hyperchromatism, though common in actively growing malignant tumours is not a constant or distinctive feature, and Feulgen's reaction shows that malignant cells do not differ significantly from normal cells in their thymonic acid content (Cowdry)

(2) Mitosis

The earlier studies of mitosis in tumours (Stroebe, 1890, Hanseemann 1890 1892, Pianese, 1896, and others) have been well reviewed by Levine (1931) who has himself made a painstaking research into the chromosome counts and the abnormalities of mitosis in tumour cells The few mitotic figures seen in benign tumours usually appear normal but in rapidly growing malignant tumours many abnormalities of mitosis are observed These include multipolar and abortive mitoses, variations in the size and number of the chromosomes, which may reach several hundred (Deckner), and are often approximately tetraploid or polyploid in number (Levine), delay and irregularity in the movements of the chromosomes and failure of cytoplasmic division, leading to multinucleated giant tumour cells Hanseemann and others have seen in these abnormalities an essential feature of neoplastic growth but this view cannot be accepted, for, as Galeotti and others showed abnormal mitoses can be produced in growing or regenerating tissues by the application of heat or chemical agents, and they are also to be seen in regenerative hyperplasia Hence, as Cowdry and others have insisted their presence in rapidly growing tumours in which of course degenerative changes are common, is not surprising

The proportion of tumour cells which are in mitosis at any given time is, in most cases, a good measure of the rate of growth of the tumour Rapidly growing tumours may show mitosis in 5 per cent or more of their cells the proportion probably never exceeds 10 per cent Although special fixatives are necessary for preservation of the finer details of mitotic figures satisfactory pictures are often afforded by the ordinary haematoxylin stained paraffin section of formalin fixed tissue (Figs 21-24) As long ago as 1890 Zenker remarked on the good preservation of mitotic figures in post mortem material and Evans (1926)

Secretion by tumours innocent or malignant of the endocrine glands is the cause of most of the hyperhormonal states e.g. acromegaly, hyperparathyroidism, adrenal virilism, hyperinsulinism and hyperadrenalism and of some cases of hyperthyroidism. Granulosa cell tumours and arrhenoblastomas of the ovary produce oestrogenic and androgenic hormones, and interstitial-cell tumours of the testis may produce precocious puberty. Chorion-carcinomas or their metastases evoke the hormonal results of pregnancy including a strongly positive Zondek-Aschheim test, persistent decidual reaction and luteal cystic changes in the ovaries. The hormonal disturbances involved in the production of the positive pregnancy reactions accompanying some malignant tumours of the testis are in need of further elucidation.

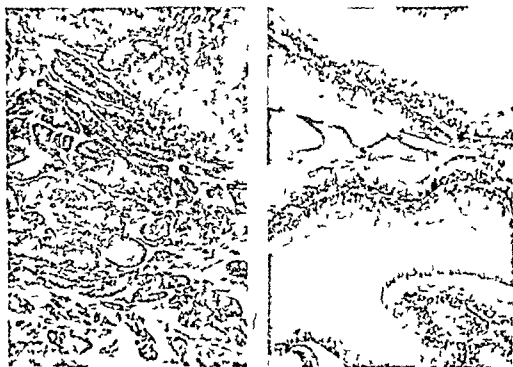


FIG. 20.—Clear-celled pseudo glandular cystic structure in a glycogen rich epidermoid carcinoma of the skin of the neck in a woman aged 72 (see p. 270). A: early glycogenic change in cancerous clump; B: cysts lined by layers of clear cells and containing watery fluid rich in glycogen ($\times 66$).

THE CYTOLOGY OF TUMOURS

(1) The nucleus

Some malignant tumours show many nuclear abnormalities including hyperchromatism, giant nuclei, lobed and multiple nuclei, abnormally large nucleoli and abnormal mitoses. Struck by these changes, many workers have adopted the view that neoplasia must consist in some peculiar change in the nucleus or in mitosis and some fantastic hypotheses have been advanced (see Chapter 11). Others have become obsessed with nuclear and nucleolar changes as a means of recognizing tumour cells. Thus MacCarty of the Mayo Clinic after studying

host animals produce the appropriate tumours, and from these characteristic cultures can be obtained. Under suitable conditions the cells of various tumours maintain their individually peculiar characters without change for unlimited periods of cultivation. As Lewis insists, the behaviour of tumour cell cultures shows plainly that malignant cells are permanently altered cells, and that they maintain their altered characters "independently of the special environment or agents which induced them."

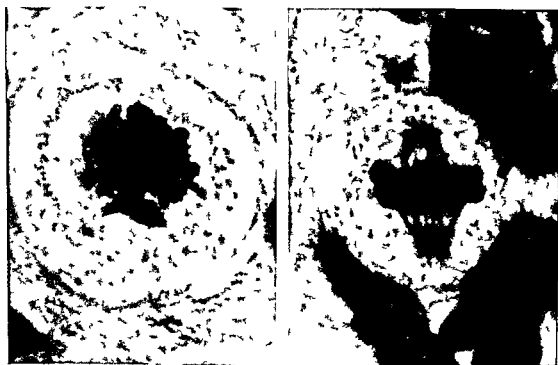


FIG. 22—Enlarged views of mitoses from the same specimen as Fig. 21. A = late spireme or aster cut in equatorial plane. B = aster figure with achromatic spindle and centrosomes ($\times 2125$).

THE STROMA OF TUMOURS

Only a bare outline of this subject can be given here, for further details, see Fischer, Bohmig and Chapter 10 of my 1934 work.

(1) The blood vessels of tumours

These comprise pre-existing vessels and newly formed vessels derived from them. As described in Chapter 9 pre-existing arteries long remain intact in invaded tissues, but veins often suffer invasion and occlusion. In many tumours the formation of new vessels from residual ones is conspicuous. In projecting papillary or fungating growths the vascular channels must clearly all be newly formed by proliferation from the vessels of the subjacent tissues. But in many non protuberant tumours also as Goldmann (1907) showed by injection methods, there is an abundant proliferation of irregularly branching small vessels at the

showed that the number of mitotic figures suffers no appreciable decrease in specimens allowed to remain unfixed for 24 hours after excision

(3) The cytoplasm

No constant peculiarities of any of the visible constituents of the cytoplasm of tumour cells have been demonstrated. Centrosomes, Golgi apparatus and mitochondria are present in malignant cells, and the variations in their appearance in some tumours are no more than might have been expected from the degrees of anaplasia or functional disturbances present (references by Cowdry)

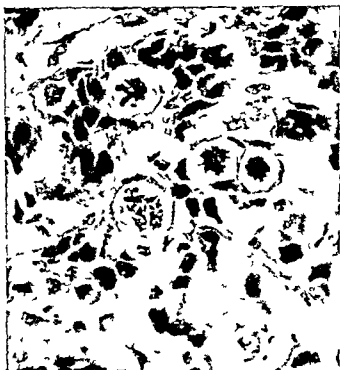


FIG. 21.—From an hepatic metastasis of a carcinoma of the tonsil showing numerous mitoses including multipolar mitoses and recently-divided paired and triple cells. (H.E. stained paraffin section of formalin fixed p.m. tissue) ($\times 600$)

(4) The tissue culture of tumours

The individual cytological peculiarities of tumours are often discernible in their cells when cultured *in vitro* and culture thus affords one important means of studying the cytology of tumours. Many studies have been made in this field foremost of which are those of Ludford and of Lewis, others will be referred to when describing the special kinds of tumours.

According to Lewis the experienced eye can distinguish the cells of different tumours in culture from one another and from the corresponding normal cells. But there is no one striking visible feature common to all malignant cells. Tumour cells in cultures show abnormalities of mitosis comparable with those seen in the tumours *in vivo*. Inoculations from tumour cultures into homologous

irregular channels lined by endothelium only or by naked tumour cells. The vascularity of course varies greatly, from the nearly complete avascularity of densely scirrhous carcinomas to the extreme vascularity of such tumours as the pulsating skeletal metastases of carcinomas of the kidney or thyroid. Many tumours, as they grow peripherally, suffer central necrosis, because of inadequate vascularity or a suicidal occlusion of vessels.

(2) The fibroblastic stroma of tumours

Nearly all tumours, innocent or malignant, possess a connective tissue framework more or less appropriate to the parenchymatous tissue proper. Such stromal tissue is scanty and devoid of recognizable arrangement in many anaplastic carcinomas and sarcomas, moderate in amount and of orderly arrangement in well differentiated malignant and benign tumours, and abnormally abundant and dense in scirrhous carcinomas.

The architecture of the fibroblastic skeleton of tumours varies with the nature of the tumours and the nature of the invaded tissues. Many carcinomas are sharply alveolated or clumped in structure, compact masses of epithelium being set in the spaces of a well defined stromal spongework. In many anaplastic growths, however, the distinction between tumour parenchyma and stroma is less clear, the tumour cells lose their polarity and the scanty residual stroma is mingled with them in a diffuse and disorderly manner.

Connective tissue is ubiquitous, and the fibroblastic proliferation (desmoplasia) evoked by a particular carcinoma is similar in most host tissues. Thus the metastases of a scirrhous carcinoma in different situations such as lung, liver, bone marrow and lymph glands, will usually show approximately similar proportions of tumour cells and fibrous stroma—another instance of maintenance of individuality by tumours. Metastatic tumours in the brain, however, often contain less fibrous stroma than their fellow metastases elsewhere, probably because of the paucity of connective tissue in the central nervous system. Infiltrating tumours in the lung often use the alveolar walls as a preformed vascular stroma, and the tumour plugs occupying the air-sacs are themselves devoid of vessels or stroma (Fig. 42).

The elastic tissue of tumour stroma was studied particularly by Scheel, Waljaschko and McConnell. The elastic fibres in the walls of vessels and ducts long resist destruction by invading growths and can be demonstrated by appropriate stains after all other pre-existing elements have disappeared. Great proliferation of elastica occurs in the dermis beneath early carcinomas of the skin (see Fig. 5) and underlying Paget's disease of the nipple and around main ducts in cancerous breasts (Sekiguchi, Cheate and Cutler), but there is usually little or no increase of elastic fibres in the stroma of invasive tumours.

(3) The osteoblastic stroma of tumours

The reaction of bone to metastatic or invading neoplasms varies greatly. In many cases the bone undergoes rarefaction and absorption, but in others it becomes denser and heavier. This osteoplastic reaction occurs very frequently from carcinoma of the prostate (qv), less frequently from mammary carcinoma and relatively rarely from other carcinomas, and, as suggested by Goetsch (1906)

margins of invading growths. By injection methods also, Lewis found that each of several rat tumours had its own peculiar vascular pattern.

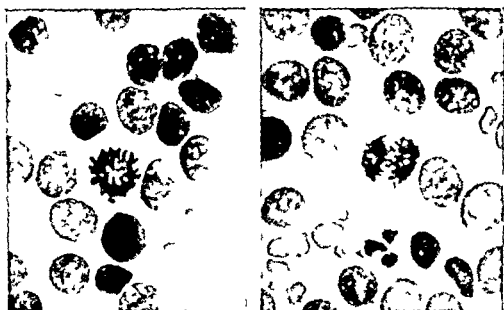


FIG. 23.—Smear of aspirated tissue from a rapidly growing tumour of soft tissues of thigh of a girl aged 16 years, probably lymphosarcoma. A = an aster. B = a diaster. The number of chromosomes, which could almost be counted, is normal or nearly normal ($\times 800$).

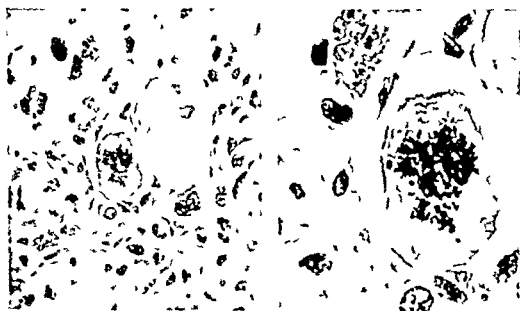


FIG. 24.—Cellular pleomorphism and mitosis in an anaplastic tumour of the lung, probably a fibrosarcoma. The chromosomes in the giant tumour cell could nearly be counted, and even in the single section greatly exceeded the normal number (> 300 and 800).

The new formed vessels in malignant tumours are usually small and simple in structure, and in rapidly growing tumours they consist of little more than

sometimes much wider. Astrocytic reaction is much more prominent in grey matter than in white, probably because protoplasmic astrocytes are more labile and responsive to stimulation than fibrillary astrocytes. The reaction zone about a metastatic growth has no "barrier" function, it is soon invaded and destroyed by the growth, while fresh reactive changes appear more peripherally. The astrocytes rarely survive for long in the substance of the growth. Oligodendrocytes appear to play little part in the reactionary gliosis around secondary tumours.

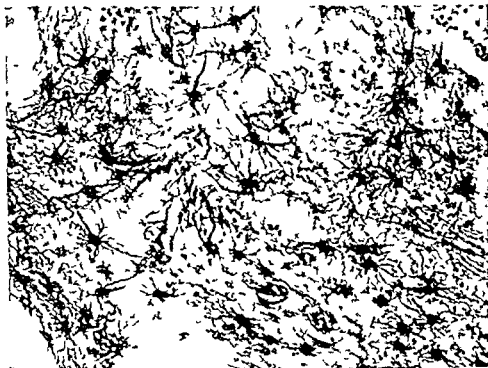


FIG. 26—Astrocytosis at the margin of a metastasis of mammary carcinoma in the brain (Cajal's gold-chloride sublimate) ($\times 150$)

The reaction of non neoplastic neuroglial cells to invading gliomas, and the persistence of such cells within the tumours, occasion great difficulties in the interpretation of the histogenesis of some of these growths (see Cox, Scherer, and Chapter 52)

(5) Leucocytic reactions excited by tumours

Excluding inflammatory infiltrates due to bacterial infections of tumours, collections of leucocytes of various kinds occur in or around malignant growths. Collections of *lymphocytes* are often conspicuous around the invading margins of squamous cell carcinomas of the lip, skin, tongue, or cervix uteri. The view, vigorously promulgated by Murphy and supported by Ewing, that this lymphocytic response is a specific defensive reaction against these tumours, has little to commend it (see Woglom 1929). *Plasma cells* often occur along with lymphocytes in the stroma of tumours and occasionally they predominate (Sormani, Willis). *Neutrophil granulocytes* often collect around necrotic foci in tumours and

and Axhausen (1909) it is probably evoked by diffusible chemical products of particular kinds of tumours. The fact that cancerous prostatic epithelium produces large amounts of an acid phosphatase suggests that the osteoplastic reaction of bone to intruding tumours is due to this or other enzymes liberated by the tumour cells.

Another form of proliferative reaction of bone to secondary growths is the deposition of new bone by expanded periosteum. This may occur either as 'onion skin' laminae more or less parallel to the surface of the bone, or as fine or coarse regular or irregular trabeculae projecting vertically from it. Both kinds of formation are well seen in metastatic neuroblastoma in bone as described and depicted in Chapter 55, but similar new bone especially of coarsely irregular vertical arrangement may form also with many kinds of metastatic carcinoma, even those with predominantly osteoclastic results (Fig 25A). This abundant new bone formation in secondary growths has often led to radiographic misdiagnoses of primary osteogenic sarcoma.



FIG. 25—Skilagrams of bones containing metastases of carcinoma of the bladder (Case 1 Chapter 28). A = humerus with metastasis containing much new formed periosteal bone. B = vertebra which though full of metastatic growth shows normal structure. Osteophytes at lower edge may have been evoked by the growth.

Another important fact for radiologists is that radiographically normal appearances may be seen in bones containing heavy metastatic growth (Fig 25B). In such bone the tumour infiltrates the marrow spaces only and leaves the trabeculae intact. There is neither osteoclasia nor osteoplasia.

(4) The neuroglial stroma of tumours

Metastatic growths in the brain often excite a neuroglial proliferation, the main elements of which are the astrocytes. Special staining methods e.g. Cuyal's gold-chloride sublimate method are necessary to display this astrocytosis adequately (Fig 26). The astrocytes multiply, become larger and their processes become coarser and more numerous. The zone of reaction varies in width; often it extends only 1 or 2 millimetres from the tumour margins but it is

as in Nicholson's and Schwenke's cases, must be taken into account in interpreting the structure of some supposedly "mixed" tumours of the uterus (*see* Chapter 48)

CARCINO SARCOMA

Good recent reviews and discussions of this controversial subject include those of Harvey and Hamilton Saphir and Vass, Foulds and Brooks 'Carcino sarcoma' implies either (a) simultaneous malignant neoplasia in two distinct tissues, an epithelial tissue and its non epithelial stroma, or (b) consequent sarcomatous change in the stroma of a carcinoma. The fortuitous development of two separate tumours a carcinoma and a sarcoma, in contiguity with each other is not relevant to the subject, and a "collision tumour" so formed should not be called a carcino sarcoma.

The evidence in support of the real existence of occasional carcino sarcomas is stronger in animal and experimental than in human pathology. The earlier experimental work which dealt with apparently sarcomatous changes taking place during successive passages of transplantable tumours, is well reviewed in the papers of Haaland (1908) and Russell (1910). Without discussing these controversial findings in any detail, I may point out that striking changes are known to occur in the histological structure of some tumours during serial transplantations, and that Lewis and Earle have found evidence in tissue cultures of the structural versatility of carcinomas. Thus Crocker tumour No 10, which was originally diagnosed as carcinoma and later assumed a sarcomatous appearance, Lewis believes may some day again be recognized as really a carcinoma. So also, Walker rat tumour 315, originally diagnosed as adenocarcinoma, on serial transplantation assumed the appearance of a round cell sarcoma, yet Lewis says "From the study of its malignant cells in cultures I am inclined to think that it is still a carcinoma." Earle described spindle celled transformation of a rat adenocarcinoma in transplants and cultures.

Another and more recent kind of experimental evidence is the production by means of chemical carcinogens of tumours which have appeared to contain both carcinomatous and sarcomatous constituents, such as those described by Bonser and Orr. Since carcinogenic hydrocarbons can evoke tumours in both epithelial and non epithelial tissues, there is of course no intrinsic impossibility in simultaneous or nearly simultaneous neoplasia occurring in two distinct tissues exposed to such agents. But, before assuming that this has indeed occurred, it is essential to consider carefully whether the supposed 'sarcomatous' element may not be only diffusely growing epithelial tissue. Some spontaneously occurring animal tumours also show a seemingly composite carcino sarcomatous structure, and Rudduck and I have reported a canine thyroid tumour which seemed clearly to be of this nature. The primary growth in the thyroid showed a mixture of adenocarcinoma and osteogenic sarcoma, while metastases in the lungs consisted of sarcomatous tissue only, specifically identifiable because of its osteoid characters.

Human pathology affords at least one indubitable example of sarcomatous change in the previously benign connective tissue of an epithelial tumour, this occasionally occurs in a mammary fibro adenoma (Chapter 13). The case is somewhat peculiar, however, in two respects first, the connective tissue of a

especially in degenerating areas of mucoid adenocarcinomas. They may invade, and be found within, large unhealthy tumour cells, a finding which has sometimes been interpreted wrongly as due to phagocytosis of the leucocytes by the tumour cells. *Eosinophil granulocytes* are sometimes plentiful in and around tumours, and general eosinophilia of the blood is present in some cases (references by Willis). The local and general eosinophil reactions of Hodgkin's disease are also to be noted here. The significance of such reactions in tumours is obscure: the functions of eosinophil granulocytes are still unknown, and collections of these cells occur in many and diverse non-neoplastic lesions. *Macrophages* laden with lipoid material or pigment, are common in or around degenerating or haemorrhagic tumours, and *foreign body giant cells* may also appear where lipoid absorption is in progress or where there are fragments of degenerating keratin or necrotic bone.

(6) Metaplasia in the stroma of tumours

Osseous or cartilaginous metaplasia in the fibroblastic stroma of carcinomas is not very uncommon. It has occurred with adenocarcinomas of the stomach (Gruber-Laubmann), of the intestine (Foulerton, Clark) of the gall bladder (Miesch), of the uterus (Nicholson-Schwenke), and of the salivary glands (q.v.). In Laubmann's case, metastases in the lungs showed osseous and cartilaginous changes in the stroma, and in Miesch's case metastases in lymph glands, liver and lungs, as well as the primary growth, showed plentiful stroma with many bony trabeculae containing bone marrow. In Schwenke's case there appeared to be a close relationship between the stromal ossification and squamous metaplasia in the tumour itself. Nicholson (1924) depicted ossification in the stroma of a carcinoma of the prostate and the formation of nodules of hyaline cartilage in the stroma of an adenocarcinoma of the endometrium. I have seen bony metaplasia of the stroma in a bronchial adenoma, and in a pleomorphic salivary tumour. Ossification or chondrification is well known in the fibrous component of mammary fibro-adenomas in dogs (Schlotthauer) and the same occurs occasionally in human mammary tumours (Cheate and Cutler-Tudhope). Foulds (1937) made a careful study of bony and cartilaginous metaplasia of the host tissues, induced by transplants of a fowl carcinoma and pointed out the significance of this regarding the histogenesis of some supposedly mixed tumours.

The occurrence of metaplasia in the stroma of prostatic carcinoma, as in Nicholson's case and of metastatic growths as in Laubmann's and Miesch's cases, points to the correct interpretation of a case described by Schmoll in 1908. This was one of prostatic carcinoma with osteoplastic metastases in many bones and metastases in the lungs which showed "osteochondrosarcomatous" tissue mingled with carcinoma. Schmoll believed that osteoplasia induced in the bones by the carcinoma had become sarcomatous and that osteosarcomatous metastases had then developed in the lungs along with metastatic carcinoma, but a preferable interpretation is that osseous and cartilaginous metaplasia took place in the stroma of carcinomatous metastases.

The possibility of stromal chondrification or ossification in uterine carcinomas

of new fibres from damaged nerves in and around tumours, but without supposing it to mean innervation of the tumour cells

That denervation of a tissue may inhibit invasive tumour growth into it, was suggested by some observations of Cheate's on the spread of rodent carcinomas of the skin, and experimental work (references by Willis, 1934) suggests that the variations in rate of growth of tumours in tissues under different states of disturbed innervation may be due to vasomotor changes. Further work is needed on this subject

RATE OF GROWTH OF TUMOURS, AND FACTORS AFFECTING IT

Different tumours differ very widely in their rates of growth. Many benign, and some malignant tumours grow very slowly and attain only a small bulk after many years, some anaplastic tumours grow with mushroom like rapidity. I have examined a metastatic deposit of a bronchial carcinoma situated in the oral mucous membrane, which grew in 4 weeks from just visible dimensions to a projecting tumour 3 centimetres in diameter and 12 grammes in weight. I have also seen patients with metastatic growths in the liver, in whom the interior edge of this organ was at palpably lower levels on several days in succession. Eveleth and Wetzel reported a case in which following excision of the lung, recurrent growth into the open pleural cavity from a small residue in the bronchial stump was found at necropsy 58 days later to have attained a weight of 2 500 grammes, a mean increase of 43 grammes daily. The authors estimated that, assuming the tumour to have grown regularly in an exponential manner, its final daily increase must have been 340 grammes, and that its rate of increase was of the same order as the maximal rate of early embryonic growth.

One of the individual characters of each tumour is its growth rate, which it tends to maintain nearly constant throughout its career. But many factors are known to be capable of modifying the standard growth rates of particular tumours. This is not surprising, for, as we have seen the high degree of structural and functional organization attained by many tumours shows that their growth is not wholly uncoordinated nor exempt from the influences governing the activities of normal tissues. Thus, tumours of tissues which are subject to hormonal control may also show evidence of similar control. As instances may be cited the acceleration of growth of carcinomas of the breast during late pregnancy and lactation and their retardation on cessation of lactation (Chapter 13) the retardation of some mammary carcinomas in mice during lactation (Haddow 1938), the temporary retrogression of some prostatic carcinomas following castration and the retardations or retrogressions of some prostatic and mammary carcinomas following administration of oestrogens (Haddow *et al*, 1944).

The most remarkable instance of alteration of tumour growth rates effected by extrinsic chemical agents is the retardation of growth produced in both experimental and spontaneous tumours by carcinogenic agents (Haddow, 1938, Haddow and Robinson 1939, Badger *et al*, 1942). Pertinent here also are the occasional spontaneous retrogressions of malignant tumours some of which appear to have followed severe infections or major operations (references in Chapter 3). It is not improbable that when more is known of the chemical changes involved in carcinogenesis, in the hormonal control of both normal and neoplastic tissues, and

fibro adenoma is not a simple stroma in the tumour but has neoplastic qualities of its own *ab initio*, the benign tumour being a genuinely mixed or composite one and secondly, sarcomatous change in this tumour is not accompanied by carcinomatous change in its epithelium so that the result is *not* a 'carcino-sarcoma', but sarcoma supervening in a fibro adenoma.

With this peculiar exception and with the exception of the equally peculiar mixed tumours of the uterus I do not know of any reported instance in human pathology in which the interpretation of sarcomatous change in the stroma of an epithelial tumour is beyond doubt. Further of the many reported cases of 'carcino sarcoma' I have not seen any which could in my opinion be accepted unreservedly. Even Harvey and Hamilton's well-considered and able advocacy of the reality of such tumours has failed to convince me. I believe that the structural vagaries of anaplastic and diffuse carcinomas and reactive changes in stromal tissues suffice to account for the appearances depicted by these and other writers. I do not deny that true carcino sarcomas may occur in human beings but no conclusively established case has been reported and most of the alleged instances are clearly only cases of pleomorphism in carcinomas.

I am not alone in this sceptical attitude. Saphir and Vass reviewed 153 supposed carcino sarcomas from the literature, and concluded 'that the carcino sarcomatous nature of these tumors is very questionable'. They also reviewed a number of their own tumours which were at first thought to be carcino-sarcomas but which on more careful examination were interpreted as primary carcinomas. Cappell described and depicted great pleomorphism in a prostatic carcinoma in which in some places the appearances were typically carcinomatous in others a sarcoma like structure was produced by diffuse growth of the carcinoma cells, while in yet other parts hyaline changes in the stroma produced superficial resemblances to cartilage and to osteoid tissue. Such appearances are readily misunderstood and in the past have given rise to much false interpretation as 'carcino-sarcoma' mixed tumours etc. The reader should recall also the paragraph earlier in this chapter on mimicry in tumours.

NERVES IN TUMOURS

In Chapter II of my 1934 work I discussed in detail the relationships between tumours and nerves and concluded with Ludford Herzog and others that there is no satisfactory evidence that malignant tumour cells are innervated that all genuine nerves found in tumours are inclusions and that supposed nerve endings in tumour cells depicted by several writers are only retraction bulbs or varicose nerve fibres contiguous with the cells. Nerves show remarkable persistence in the substance of invading tumours so that all manner of relationships between residual nerve fibres and tumour elements will be demonstrable.

Moreover when a nerve trunk is damaged by a tumour numerous new fibrils grow from the living axis cylinders of the proximal stump of the nerve trunk. These new axis cylinders not only grow within the perineural tube of the proximal portion but penetrate into the neoplastic tissue. The process is exactly similar to what occurs after section of a peripheral nerve, and there seems no reason to suppose that the new formed axis cylinders exert any trophic influence on the neoplastic cells. (Rytic) Meissel also saw this regenerative outgrowth

as regards all of these substances, different workers have obtained very diverse results, no doubt because of differences in the nature of the tumours analysed and in the amount of the secondary changes present in the tissue. Voegtlin decided that "no conclusive evidence exists at present which reveals any quantitative difference in chemical composition between normal and malignant tissues. Whatever differences do exist are of a quantitative nature, the biological significance of which is difficult to evaluate."

(2) The carbohydrate metabolism and respiration of tumours

Warburg's early work in this field was summarized by him in 1925 and by Dickens in 1930. Warburg's technique permitted estimation of the tissue respiration (oxygen consumption) and glycolysis (the splitting of sugar into lactic acid) in thin slices of fresh tissue. He found that many normal tissues, especially actively proliferating ones, and also actively growing tumours, showed marked glycolytic activity under anaerobic conditions, that under aerobic conditions the glycolytic function of normal tissues was suppressed in favour of oxidation, but that tumour tissue often showed aerobic glycolysis. A characteristic feature of the metabolism of tumour cells appeared to be their high power of glycolysis under aerobic as well as anaerobic conditions with low respiratory quotient, and this was attributed to some disorder of oxidation in the cells (Dodds).

Subsequent work, however, has shown that aerobic glycolysis is not peculiar to tumours, but is exhibited also by many normal tissues, e.g. testis, retina, tonsil, kidney medulla, intestinal mucosa and bone marrow, and that some malignant tumours e.g. some human lymphosarcomas and mammary carcinomas, show low aerobic glycolysis. Interesting discussion of the *pros* and *cons* of the question will be found in the letters of Dickens, Boyland and others in *Nature* (1940), in which Berenblum *et al.* concluded that 'when a tumour is compared with the tissue from which it is derived, there are no characteristic differences or peculiarities between the carbohydrate metabolism of the two'. Orr and Stickland (1941), however, found that in tumours arising in the rat's liver following administration of azo dyes there was a sudden change in metabolism as compared with that of the non-cancerous liver tissue.

It is clear that many actively growing tumours do show high aerobic and anaerobic glycolysis and low R.Q. though these are not peculiar to tumours. The high aerobic production of lactic acid by some tumours has been shown *in vivo*, when fasting tumour-bearing animals were given intraperitoneal injections of glucose, fructose or maltose, a striking decrease of pH values was shown by means of an electrode introduced into the tumours (Voegtlin). Fructose is said to be glycolysed by some tumours but not by others (references by Boyland).

(3) Constitutional metabolic effects of tumours

In Chapter 3 it was pointed out that cachexia accompanying malignant tumours is readily explicable as the result of ulceration, haemorrhage, pain and interference with important bodily functions, and that no specific cancerous poisons need be postulated. Study of the chemistry of tumours confirms this, no peculiar constituents or metabolites have been identified in tumours. Most of the laborious work done on the chemistry of the blood and other body fluids and tissues in cancer patients or tumour-bearing animals has been wasted effort.

in tumour metabolism these may all be seen to be related phenomena and perhaps radiational carcinogenesis and radiational therapy may also be found to come within the same ambit. The hope of the therapist is that future research may discover some chemical substance or other agent capable of body wide application, which will be much more selectively lethal or inhibitory to tumour tissue than any yet known. If such a discovery is made, it will be as the result of more intimate probing of the chemistry of carcinogenesis, tumour inhibition and hormone action.

THE CHEMICAL COMPOSITION AND METABOLISM OF TUMOURS

Although variable quantitative chemical and metabolic differences between some normal and neoplastic tissues have been detected it is doubtful whether these have any great significance as regards the nature and genesis of neoplasia. Only the barest outline of the main findings can be attempted here for further details and references see the reviews of Boyland (1934), Holmes (1935), and Voegtlin (1937).

(1) The chemical composition of tumour tissue

A great deal of the work in this field is valueless because of unsuitably chosen material or lack of adequate normal controls. Tumours with abundant stroma or rich in blood or oedema fluid, or containing plentiful secretions or showing haemorrhages, degenerative changes or necrosis or accompanied by plentiful aggregations of inflammatory or phagocytic cells—all of these are clearly unsuitable for chemical analysis and comparison with normal tissues. Yet very few recorded analyses make it clear that these sources of error were appreciated and avoided. And how difficult it must be to avoid them will be recognized by every pathologist familiar with the diversity of microscopic structure and cellular health in malignant tumour tissue. When he observes how frequent lipoid degenerative changes and lipoid phagocytosis are in tumours when he knows that tumour cells commonly produce their appropriate secretions in great quantities when he sees the large amounts of glycogen or pigments or mucin or of calcific deposits present in certain tumours, he will attach little importance to the results of painstaking analyses of the cholesterol esters or enzymes or proteins or carbohydrates or inorganic salts of tumour tissues or to comparisons of these with analyses of the corresponding normal tissues. Further as regards most tumours it is not possible to obtain the corresponding normal tissues for comparison. The normal tissues corresponding to carcinoma of the breast, sarcoma of bone and glioma of the brain are mammary epithelium, osteoblasts and astrocytes respectively and none of these can be obtained for analyses unmixed with other tissue elements except in the unnatural conditions of tissue cultures.

With the foregoing points in mind it is not surprising to learn that several workers cited by Boyland and Voegtlin have found that many tumours have a relatively high lipoid content, that tumours differ in the amounts of sodium, potassium, calcium and magnesium which they contain but that there are no constant or significant peculiarities (Sherr) that various enzymes and vitamins, glutathione, pyruvic acid and many other substances present in normal tissues are present also in tumours in variable non-distinctive amounts and that

- Haddow, A and Robinson, A M (1939) *Proc Roy Soc Lond B* 127 277
- Haddow A, Watkinson J M Paterson E and Koller, P C (1944) *Brit Med J*, ii 393
- Hansemann D (1890 1891 and 1892) *Virchows Arch*, 1890, 119, 299, 1891, 123 356, 1829 129 436
- HARVEY, W F and HAMILTON, T D (1935) Carcino sarcoma *Edinb Med J*, 42 337
(The most important recent paper upholding the opinion that human carcino-sarcomas exist)
- Holmes B E (1935) *Annual Rev Biochem*, 4 469
- Kettle E H (1925) *The Pathology of Tumours* London
- Laubmann W (1932) *Virchows Arch* 285 169
- LEVINE, M (1931) Studies in the cytology of cancer' *Amer J Cancer* 15, 144 788 1410
(An excellent review of mitosis in tumours with careful personal studies of chromosome numbers and many fine photographs)
- LEWIS, W H (1936) *Malignant Cells*, The Harvey Lectures p 214 (An excellent outline of the cultivation of tumour cells)
- LUDFORD, R J (1934) 'Structure and behaviour of the cells in tissue cultures of tumours', *Imp Cancer Res Fund Sci Rep*, p 147 (A valuable review)
- MacCarty W C (1936) *Amer J Cancer* 26 529
- Meissel M N (1933) *Z Krebsforsch* 39 128
- MICSEH G (1933) Knochenbildung im Gallenblasenkrebs und in seinen Metastasen, *Frankfurt Z Path* 44 430 (An excellent report)
- Murphy J B and others (1921) Several papers *J Exp Med* Vol 33
- NICHOLSON G W (1921 1924 and 1933) Studies on tumour formation *Guy's Hosp Rep* Nos I VIII and XII and *The Nature of Tumour Formation* 1926 (Nicholson has voiced the strongest protests against the view that tumours lack organization)
- Orr J W and Stickland L H (1941) *Biochem J*, 35 479
- Panton P N (1937) *Lancet* i 793
- Pianese G (1896) *Beitr path Anat Suppl* 1
- Reimann S P and Toennies G (1940) *Arch Path* 29, 175
- Rudduck H B and Willis R A (1938) *Amer J Cancer*, 33 205
- Russell B R G (1910) *J Path Bact*, 14 344
- Ryrie G M (1933) *J Path Bact* 36 13
- SAPHIR, O, and VASS, A (1938) Carcino sarcoma *Amer J Cancer* 33 331 (An important critical review)
- SCHERER, H J (1938) Structural development in gliomas *Amer J Cancer* 34 333
(This and Scherer's other studies show the importance of the pre-existing structures in determining the architecture of the tumours)
- Schlotthauer C F (1940) *J Amer Vet Med Assoc* 96 632
- Schmorl (1908) *Verh Dtsch path Ges* 12 89
- Schwenke A (1932) *Z Geburts Gynak* 103 592
- Sekiguchi S (1917) *Ann Surg* 65 175
- Shear M J (1933) *Amer J Cancer* 18 924
- Sorman B P (1906) *Virchows Arch* 184 177
- Stroebe H (1890) *Beitr path Anat* 7 339
- Tudhope G R (1939) *J Path Bact* 48 499
- Tudhope G R and Chisholm A E (1934) *J Obst Gyn* 41 708
- VOEGTLIN, C (1937) Biochemistry of malignant tissues, *Physiol Rev*, 17, 92 (A useful review)
- Warburg O (1925) *J Cancer Res* 9 148
- Warburg O (1930) *The Metabolism of Tumours* (translation by F. Dickens) London
- Willis R A (1932) *J Path Bact* 35 11
- Willis R A (1932) *Med J Austral* ii 65
- WILLIS, R A (1934) *The Spread of Tumours in the Human Body* (Chapters VII X and XI contain fuller details of many of the subjects discussed in the present chapter)
- Woglom W H (1929) *Cancer Rev* 4 129
- Woodhouse D L (1940) *Amer J Cancer* 40 359
- Zenker K (1890) *Virchows Arch* 120 68

any abnormalities found have been no more than non specific secondary effects of the tumours. The hope that biochemical studies of the cancerous patient will reveal anything fundamental regarding the nature or growth of cancers or will lead to diagnostically useful tests, has so far proved a vain one, and is likely to remain so.

Of the 30 or more tests which have been advanced for the chemo diagnosis of cancer reviewed by Panton (1937) and Woodhouse (1940) many have been patently absurd, and none has proved of any real use. To the pathologist, aware of the diversity of diseases included under the term 'cancer', the discovery of any generally applicable chemical 'test for cancer' would indeed appear little short of miraculous. One might as well seek for a universal 'test for inflammatory diseases'.

REFERENCES

- Axhausen G (1909) *Virchows Arch* 195 358
 BADGER G M, ELSON, L A., HADDOW, A., HEWETT, C L and ROBINSON A M (1942) The inhibition of growth by chemical compounds *Proc Roy Soc Lond B* 130 255
 BOHMIG R (1930) Das Krebsstroma und seine morphologischen Reaktionsformen, *Beitr path Anat* 83 333 (An excellent account of the stroma of tumours)
 Bonser G M and Orr J W (1939) *J Path Bact* 49 171
 Boyland E (1934) *Annual Rev Biochem* 3 400
 Brooks S M (1943) *Arch Path* 36 144
 Cappell D F (1935) *Glasgow Med J* 124 177
 Cheate G L (1903) *Brit Med J* 2 1515
 Cheate G L and Cutler M (1931) *Tumours of the Breast* London
 Clark A (1935) *Brit J Surg* 22 889
 Cohn M (1926) *Virchows Arch* 259 30
 COWDRY, F V (1940) Properties of cancer cells *Arch Path* 30 1245 (A valuable review)
 Cowdry E V and Paletta F Y (1941) *J Nat Cancer Inst* 1 745
 Cox L B (1933) *Amer J Path* 9 839
 Deckner K (1938) *Z Krebsforsch* 48 129
 Dickens F, Boyland E and others (1940) *Nature* 145 512, 513 778 and 779
 Dodds E C (1931) *Amer J Cancer* 15 2765
 EARLE W R (1935) A study of the Walker rat mammary carcinoma 256 *in vivo* and *in vitro* *Amer J Cancer* 24 566
 Evans N (1926) *Arch Path* 1 894
 Eveleigh M S and Wetzel N C (1941) *Cancer Res* 1 721
 Ewing J (1940) *Neoplastic Diseases* Philadelphia
 Fischer W (1929) *Verh Dtsch path Ges* 24 263
 FOULDS L (1940) The histological analysis of tumours. A critical review *Amer J Cancer* 39 1 (Contains valuable discussions of tumour structure, stroma, individuality and carcino sarcoma)
 Foulds L (1937) *J Path Bact* 44 1
 Foulerton A G R (1905) *Lancet* ii 1827
 Galeotti G (1893 and 1896) *Beitr path Anat* 1893 14 288 1896 20 192
 Geschickter C F and Lewis D (1938) *Brit Med J* i 499
 Goetsch W (1906) *Beitr path Anat* 29 218
 Goldmann E (1907) *Proc Roy Soc Med* 1 (Surg Sect 1)
 Grauer R C and Robinson G H (1932) *Amer J Cancer* 16 191
 Gruber G B (1913) *Beitr path Anat* 55 368
 Haaland M (1908) *Imp Cancer Res Fund Sci Rep* p 175
 Haddow A (1938 and 1939) *J Path Bact* 1938 47 553 1939 47 567 581

THE INVASIVE PROPERTIES OF TUMOUR CELLS

Properties of the tumour cell itself, known or hypothetical, which may be of significance as regards its invasive capacity include (1) its power of progressive multiplication, (2) its motility (3) its possible phagocytic powers, and (4) its possible elaboration of toxic or lytic substances. To these must be added another possible factor residing not in the tumour cell itself but in its environment namely (5) the possible loss of growth restraints normally exercised by neighbouring tissues on each other. Let us examine each of these in turn.



FIG. 27—A metastasis of anaplastic carcinoma of parotid gland in lung showing compression of lung, good demarcation of edge of growth but absence of a capsule ($\times 100$)

(1) Progressive multiplication

Progressive multiplication of malignant tumour cells is certainly an important factor in their infiltrative growth. At the margins of an invading tumour successive generations of young cells are continuously budded out into the surrounding tissues and at the same time, expansive increase of the main mass of the growth must provide a *vis a tergo* which assists to thrust the budding marginal cells into all available crevices of the invaded tissues. The growth of the tumour thus resembles that of a root and its attached rootlets, the main root enlarges expansively, while the rootlets and root hairs thrust their way along lines of least resistance in the surrounding soil, and the growth and soil disrupting powers of the whole structure are attributable to the progressive proliferation of its cells.

However, while proliferation is an important factor in invasive growth it is certainly not the only or even the most essential one. There are some rapidly proliferating tumours with no invasive properties such as the rapidly growing mammary fibro adenomas, and there are many carcinomas of relatively slow growth which are nevertheless highly infiltrative such as some scirrhous carcinomas of the breast or stomach. Further, the often rapid cellular multiplication of reparative and hyperplastic tissues or of transplanted embryo tissues, confers no invasive properties.

CHAPTER 9

THE DIRECT SPREAD OF TUMOURS

IN CHAPTER 7 we saw how in the early development of a tumour, we must distinguish between spreading neoplastic change in a field of tissue and cellular proliferation of the neoplastic tissues. During the early growth of a tumour, these two distinct processes coexist but after the whole of the predisposed field has undergone neoplastic change the tumour grows solely by multiplication of its own cells. This proliferative growth continuously increasing the bulk of the tumour tissue, progresses in one or both of two ways with respect to neighbouring normal tissues namely (1) *expansive* and (2) *infiltrative*.

(1) Growth by expansion

Growth by expansion, whereby a circumscribed tumour merely thrusts neighbouring tissues aside as it enlarges, calls for little detailed description. Purely expansive growth as with many kinds of benign tumours produces a sharply circumscribed tumour often distinctly encapsulated. In malignant tumours all degrees of combination of expansive and infiltrative growth are seen and when the former predominates, the tumour may appear to the naked eye to be sharply circumscribed around most or all of its periphery as for example with many renal carcinomas. In such cases however, closer study usually reveals indistinct naked eye demarcation or microscopic degrees of infiltration at some part of the margin of the growth (Fig. 27).

While a tumour growing wholly or largely by expansion in a homogeneous tissue will usually be nearly spherical in shape one growing in heterogeneous tissues or in situations where it is subjected to unequal pressures in different parts will be moulded into different shapes. Thus subcutaneous lipomas are usually more or less flattened because confined between the skin and the underlying part, multiple uterine myomas suffer deformations by mutual compression, circumscribed tumours projecting into hollow viscera often become elongated or otherwise moulded in shape by the cavities in which they grow and physically dense or rigid structures such as bones ligaments, tendons or stout visceral capsules confine and deform expanding tumours contiguous with them.

(2) Growth by infiltration

Growth by infiltration, whereby the multiplying cells of a tumour insinuate themselves into the minute interstices of the normal tissues requires much more detailed description. We have to consider on the one hand the invasive properties of tumour cells and on the other hand the paths by which infiltration takes place and the changes brought about by such infiltration. This is the special subject of the present chapter. (For additional details see Chapter 1 of my 1934 work.)

(3) Phagocytic powers

The phagocytic powers of tumour cells, displayed for foreign particles by some kinds of motile cells in culture, are of little significance as regards the invasiveness of tumours. Steinhaus, Stroebe and others depicted appearances suggesting that tumour cells had engulfed blood corpuscles or stromal cells, but, as Greenough showed, most of the "cell inclusions" often seen in tumours are products of the cells themselves and not the remains of enclosed cells. Occasionally, polymorphonuclear leucocytes are found within tumour cells, I have seen this most frequently in mucoid carcinomas, and it clearly denotes, not phagocytic ingestion of the leucocytes by the tumour cells, but invasion of degenerating or unhealthy tumour cells by the leucocytes.

(4) Metabolites

Metabolites capable of affecting the surrounding tissues are undoubtedly produced by tumours. The high lactic acid output of rapidly growing tumours is well known and the stromal reactions evoked by invading tumours point to the influence of diffusible products of the tumour cells. According to Voegtlin, "It is conceivable that the excessive amounts of lactic acid present in tumours with the consequent decrease in pH may be concerned in the destructive action of tumour cells on adjoining normal tissue". However, there is no evidence that slowly growing tumours show any significant metabolic differences from the corresponding normal tissues, or that any tumours produce abnormal metabolites with toxic or lytic properties. The degenerative and atrophic changes in the cells of tumour invaded tissues are readily accounted for as the result of mechanical pressure, vascular disturbances, and unsuccessful nutritive competition with the continuously multiplying invading cells. The idea that tumour invasion depends essentially on damaging effects exerted on the invaded tissues by soluble products of the tumour cells is entirely speculative.

(5) Possible loss of growth restraints

Release from growth restraints was postulated by Ribbert as the essential factor in invasive malignant growth. Ribbert assumed that the capacity of most normal cells for indefinite multiplication was normally restrained by a complex set of factors largely dependent on the organized relations of the cells to adjacent tissues. Release from these restraints e.g. as the result of inflammatory isolation of groups of epithelial cells, permitted these cells to multiply continuously and to invade, thus forming a malignant tumour. Plausibility was lent to this view when tissue culture experiments not only proved the unlimited proliferative powers of normal cells but also showed the mutual organizing influence of epithelia and connective tissues when grown together.

However, while it is quite possible that in the early genesis of a primary carcinoma connective tissue changes may play some part in facilitating epithelial invasion, there are good grounds for rejecting the hypothesis of impaired stromal restraints as an adequate general explanation of the proliferative and invasive properties of tumours. (a) The cells of a primary growth continue to invade neighbouring tissues to depths far beyond the extent of stromal changes due to the carcinogenic stimuli which evoked the growth. (b) When transferred to

(2) Motility

The motility of some kinds of tumour cells is well attested. Virchow (1863), Grohe (1865) and Carmalt (1872) long ago observed amoeboid movements of cells from freshly excised tumours, and Waldeyer (1872) and Vierth (1895) pointed out the possible importance of such motility in tumour infiltration and metastasis. While it is possible that these early workers mistook migrating macrophages for tumour cells, later tissue culture studies have shown that certain kinds of neoplastic cells can migrate. The earlier observations of Carrell and Burrows, Hanes and Lambert, and Lambert in this field have been confirmed by more recent workers, e.g. Lewis, Ludford, Cox and Cranage, Russell and Bland, and Coman.

Just as the most actively migratory cells in cultures of normal tissues are those of the macrophage fibroblast series of mesenchymal tissues (Ludford) so also the most active motility observed in tumour cells is in those of mesenchymal tumours. Bland and Russell vividly described the movements of meningioma cells in cultures as follows: 'They glide forward like slugs trailing behind them a single triangular or tapering process and throwing forth in front a number of mobile flame shaped processes which appear to be feeling their way through the medium.' The characteristic form of migration is in the shape of a growing tongue or spike of cells which slip along one over another with their sides always in apposition, each cell using the other as a scaffold along which to creep. Cinematography of the epithelioid sheets in both meningioma and foetal leptomeninges shows that the cells move about independently in them and crawl about on top of one another.

No doubt, in tumours derived from the normally migratory cells of the haemopoietic tissues free cell motility is commonly present, and this may easily be an important factor in the wide diffusion of malignant cells in the leukaemias and generalized lymphosarcomatosis.

Active migration of the cells of gliomas of various types in tissue culture was described by Russell and Bland. Of tumour astrocytes they said, 'They are able as units to move freely in an amoeboid fashion and to regain their more elaborate form on coming to rest.' These potentialities doubtless explain in some measure the highly infiltrative character of the gliomas.

The evidence for free cell motility in epithelial tumours however is inconclusive. Neoplastic like normal epithelia in culture, usually form compact sheets of cells from which isolated cells seldom migrate, and from the structure of well differentiated squamous-celled or glandular carcinomas, it also seems unlikely that they possess independent migratory cells. However, Coman (1942) observed that in tube cultures of some carcinomas cells might become detached from the main mass, display amoeboid movement and form new isolated colonies. The same worker (1944) also advanced micro dissectional evidence that squamous carcinoma cells have subnormal adhesiveness, which might conceivably be related to their invasive properties. Further studies are needed to ascertain whether the poorly differentiated cells of anaplastic carcinomas may often be motile in fresh tissues or cultures.

the *tout ensemble*, different but more or less fixed for every type of malignant cell, that counts" It must be admitted, however, that so far the main components of the *tout ensemble* remain obscure

THE ROUTES OF INVASION

Infiltrating tumour cells take the following paths (1) tissue spaces, (2) intracellular paths, (3) lymph vessels, (4) veins and capillaries, (5) arteries, (6) coelomic spaces, (7) cerebrospinal spaces, and (8) epithelial cavities



FIG 29 —Interstitial infiltration of wall of a vein by spheroidal-cell carcinoma of breast ($\times 40$)

(1) Infiltration of tissue spaces

Microscopically it is often clear that the cells of a tumour have infiltrated the tissue spaces or intercellular interstices dissecting the tissues apart along planes of anatomical cleavage and occupying all available nooks and crannies amongst the tissue elements. Tumour cells are seen in immediate contact with muscle fibres, parenchymatous epithelial cells, or nerve cells (Figs 28, 29). This is indeed the initial and fundamental mode of infiltration, a carcinoma does not at once penetrate to the lumina of lymphatics and blood vessels, it must first infiltrate tissue interstices. So also the peripheral extension of well established growths continues to be partly or largely by a general infiltration of tissue spaces, not restricted to vascular channels or other preformed paths. This is not to deny that infiltration often involves lymphatics and blood vessels as well as general intercellular spaces, or that some tumours spread preferentially by vascular channels.

As might be expected, invasive growth progresses most rapidly in soft tissues with many potential or actual interstices, such as muscular tissue, the parenchyma of most viscera, central nervous tissue, or bone marrow. On the other hand,

other sites and tissues of the body by metastasis the cancerous cells continue to display the invasive properties undiminished, properties which are *not* displayed by grafts of normal tissue experimentally transferred to the same sites (c) The unimpaired invasiveness of malignant tumours when transplanted from one animal to another shows that this cannot depend on any hypothetical loss of tissue restraints peculiar to the first animal (d) Tumours of identical origin show widely different invasive powers, and the particular degree of invasiveness displayed by a given tumour reappears repeatedly in its metastases and in the case of transplantable tumours, in repeated transplants. Each tumour maintains its own peculiar infiltrative and metastatic proclivities (e) Pure cultures of cells *in vitro* have clearly been removed from all restraints exercised by other tissues but, cultures of normal cells do not grow into tumours when implanted



FIG 28—Interstitial infiltration of muscular coat of small intestine by argentaffin carcinoma ($\times 32$)

into homologous animals while cultures of malignant cells of the same type produce tumours when implanted. It is clear then that the invasive properties of tumours reside largely or entirely in the tumour cells themselves. As Foulds said, 'There is no evidence that normal cells of any age have the capacity for behaving like cancer cells under any known conditions.

We must conclude then that the factors determining invasiveness in a tumour are still undetermined. Continued excessive proliferation is one of them but not the sole one. Mutual adhesiveness or possibly other physical properties, of the tumour cells may be concerned. Motility of tumour cells may play a part in some kinds of tumours. While diffusible metabolites from tumour cells may effect changes in neighbouring tissues, there are no solid grounds for regarding these changes as the essential prelude to invasion. Malignant invasion cannot be explained as the result of release of restraints exercised by neighbouring tissues. Invasiveness is clearly a property of the tumour cell itself. Perhaps invasiveness does not depend on any single factor perhaps as Cowdry concludes. It is

of the histological study of tumours. Of the earlier accounts of this mode of spread, those of Waldeyer (1867), Hoggan (1878) and Recklinghausen (1885) are notable, while for clarity and completeness those of Heidenhain (1889), Vogel (1891), Stiles (1899) and Ernst (1905) have not been bettered. Handley (1922) attributed to lymphatic permeation an exaggerated pre-eminence in tumour spread and metastasis which, though widely accepted in surgical teaching, is not endorsed by most pathologists (*see* Goldmann, 1911, Willis, 1934, and Gray, 1938).



FIG 31 —Permeation of perineural lymphatics by spheroidal cell carcinoma of breast ($\times 40$)

Striking naked eye examples of lymphatic permeation are often to be seen in the serous membranes, the affected area presenting clearly visible white networks or strands of growth occupying and distending the subserous lymph vessels. The best specimens of this are seen in the visceral pleura in some cases of primary or secondary carcinoma of the lungs and in the mesentery in some cases of secondary peritoneal carcinosis. In most cases of this kind there is a coexisting permeation of the visceral lymphatics, e.g. extensive subpleural lymph vessel carcinosis of the lungs is always accompanied by widespread permeation of the peribronchial and septal lymphatics, often visible on the cut surface as fine nodular branching strands. Such affection of the lung which is well described and depicted by Wu, is most often secondary to carcinoma of the stomach, but is seen also from carcinomas of the breast, uterus, intestine or lung itself. Occasional cases of cutaneous melanoma display striking naked eye examples of lymphatic permeation, the affected vessels appearing as black cords between the primary growth and the regional lymph glands (Marchand, Handley, Hertzler and Gibson, Sutton and Mallia).

Microscopic examination of the infiltrating margins of carcinomas often reveals good examples of the growth of tumour cells along perineural perivascular

densely compact tissues with few interstices such as cartilage or dense fibrous tissue, act as more or less effective barriers to invading tumours. Thus tendons, ligaments, fasciae the sclera strong visceral capsules periosteum and articular and other cartilages often remain intact in invading tumours, or confine and mould them.

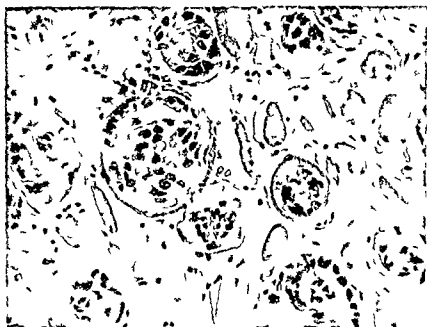


FIG. 30—Invasion of skeletal muscle fibres by carcinoma of lung ($\times 280$)

(2) Intracellular infiltration

Occasionally tumour cells are seen to have penetrated within the cytoplasm of the cells of the invaded tissues. Such intracellular invasion occurs most frequently into striated muscle fibres and rarely into epithelial cells or nerve cells.

Invasion of muscle fibres occurs usually along with interstitial infiltration but is sometimes the predominant mode of extension in the muscle. The malignant cells penetrate the sarcolemmal sheaths and multiply within the striated substance of the fibres. The sarcolemma long persists as a distended investing sheath for the cylinder of growth which has replaced the fibre substance. Often the cells advance axially along the fibre leaving a residual zone of muscle cytoplasm beneath the sarcolemma (Fig. 30). Examples of this mode of extension are recorded by Fujinami, Speed, Willis, Pulvertaft and Hartz and van der Sar.

Invasion of epithelial cells or of columns of cells is best exemplified in the extension of some secondary carcinomas in adrenal cortical tissue (Willis, 1934), rarely such invasion may be detected also in the liver or kidney.

(3) Infiltration along lymph vessels—lymphatic permeation

Lymphatics constitute a system of preformed paths of which many carcinomas freely or even preferentially avail themselves. The part played by lymph vessels in the direct extension of carcinomas was recognized almost from the beginning

of breast cancer with widespread permeation and skin nodules on the trunk, the cervical, axillary, inguinal, and often also the thoracic and abdominal lymph glands are cancerous, and extensive lymph vessel carcinosis of the pleura and lungs or of the peritoneum is always accompanied by involvement of the thoracic or abdominal lymph glands. Hence the absence of lymph nodal deposits in a region of secondary growths thought to have arisen as a result of lymphatic permeation is strong evidence that this interpretation is erroneous. This test proves, for example, the falsity of the view of Handley, Kolodny and others that metastatic growths in bones arise by way of neighbouring lymphatics, for, as I pointed out in 1934 and as my subsequent observations confirm, most metastatic growths in the skeleton are *not* accompanied by tumour deposits in the regional lymph glands.



FIG. 33 — Permeation of perineural lymphatics by adenocarcinoma of gall bladder ($\times 90$)

The fate of cancerous lymphatics has been the subject of some debate. Handley described a perilymphatic fibrosis which obliterated the vessels and destroyed their tumour content so that the spreading permeation zone became separated from the parent primary growth by a widening zone of cancer free fibrosed tissue. Along with Fitzwilliams, Fraser and most other workers, I have seen no evidence of such a process.

Lymphatic permeation is not confined to small vessels, but occurs frequently also in vessels of large calibre such as the main tributaries of the cisterna chyli and thoracic duct or the cisterna and duct itself. The earlier records of tumour invasion of the thoracic duct were collected by Leydhecker (1893), Winkler (1898) and Schwedenberg (1905), and in 1934 I fully reviewed the subject. The duct is invaded in about 3 per cent of all fatal cases of malignant disease, and in at least 6 per cent of all fatal cases of abdominal carcinomas. Invasion almost always takes place from tumour deposits in the upper retroperitoneal lymph glands either directly or by way of the main lumbar or mesenteric tributaries of the cisterna. Carcinoma of the stomach is the responsible primary tumour in about one third of the cases, carcinoma of the uterus in about one quarter

or interstitial lymphatics (Figs 31-34). In most cases such microscopic permeation extends only for short distances beyond the edges of the visible or palpable tumour, with some tumours however it is surprisingly extensive. Thus from a relatively small palpable growth in the breast, impalpably permeated lymphatics, perhaps indicated by scattered outcrop nodules in the skin, may ramify widely over the trunk and even on to the proximal parts of the limbs. Small gastric carcinomas may produce almost body wide permeation of lymphatics. I have seen a carcinoma of the parotid gland with permeation of the dermal and deep fascial lymphatics accompanied by outcrop nodules in the skin of the trunk and thighs (Case No. VI, Chapter 17, and Willis 1934).

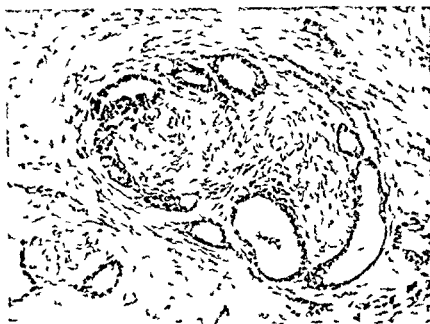


FIG. 32.—Permeation of perineural lymphatics by adenocarcinoma of stomach ($\times 120$)

However such extensive lymphatic permeation does not usually proceed in a simple centrifugal manner from a single primary focus. In cases of mammary cancer with widespread permeation and skin nodules as also in my case of parotid cancer just cited, it is certain that tumour occlusion of regional lymph glands and main lymph vessels occasions repeated retrograde embolic dissemination of the tumour cells in plexus lymphatics thus establishing auxiliary foci and satellite nodules from which permeation extends to link up with other permeated areas. So also widespread permeation from gastric and other visceral growths proceeds not only from the primary tumours but from many metastatic foci established in lymph glands, peritoneum or other organs. Extensive lymphatic permeation is rarely or never a simple centrifugal process but depends on confluence of separate zones of permeation from subsidiary foci established by metastasis.

The condition of lymph glands in an area of presumed lymphatic permeation is of great significance. In a region of extensive permeation of lymph vessels it is clearly inevitable that all lymph glands in the region should be affected either by continuous permeation or by embolism. Experience confirms this in cases

The frequency with which gross tumour invasion of large veins is demonstrable at necropsy is insufficiently appreciated. In 500 consecutive necropsies on cases of malignant disease of all kinds (Willis, 1941), I found naked eye examples of invaded veins in 102 cases (20 per cent). This, of course, is a decided under estimate, since it was impracticable to make a complete dissection of all veins in affected areas. In a series of 64 necropsies on cases of epidermoid carcinoma of the head and neck, in which careful dissection of all main veins in this region were undertaken, these veins were found grossly invaded in 30 cases (46 per cent). A detailed account of the first 20 cases in this series was published in 1930

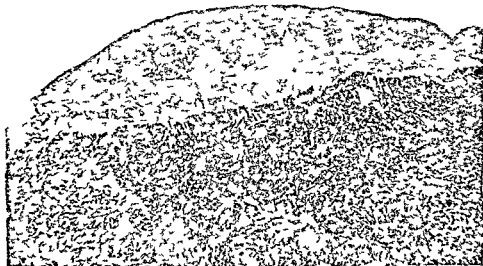


FIG 35—A low mound of thrombus formed over area of invasion of lumen of a main hepatic vein by a metastasis of carcinoma of lung. The thrombus itself contains colonies of tumour cells ($\times 10$)

In 1934, I collected from the literature examples of invasion of large veins by tumours of all kinds. Carcinomas of the stomach, pancreas, liver, lung, thyroid and kidney often invade main veins, as do also embryonic renal tumours, testicular teratomas, chondrosarcomas and other sarcomas. The invading tumours sometimes grow along the lumen of the veins for surprising distances, e.g. renal carcinomas invading the renal veins may grow up the inferior vena cava and into the right chambers of the heart (references by Polayes and Taft), chondrosarcomas have extended in continuity through the vena cava and right cardiac chambers into the pulmonary arteries (Fry and Shattock, Kosa) and the same has been observed of testicular tumours. Probably the most extensive intravascular growth recorded was from the teratoma of the testis described by Herzog, this formed a continuous irregular cast occupying the vena cava, renal veins, right chambers of the heart, and the pulmonary arteries even to their peripheral branches.

The structural details of invasion of veins were first studied carefully by Goldmann and later by myself (1930 and 1934). Purely mural invasion of a large vein may set up a proliferative thickening of its intima which, along with mechanical

of the cases, while the remainder include carcinomas of the intestine, gall bladder ovary and other abdominal and pelvic viscera, and only occasionally pulmonary, oesophageal or other growths affecting the duct in its thoracic part. The tumour may occupy and distend the duct in part or the whole of its course, and the cylindrical or fusiform mass of growth may attain a diameter of 1 or 2 centimetres



FIG. 34.—Permeation of large lymphatics in wall of duodenum by adenocarcinoma of stomach ($\times 120$)

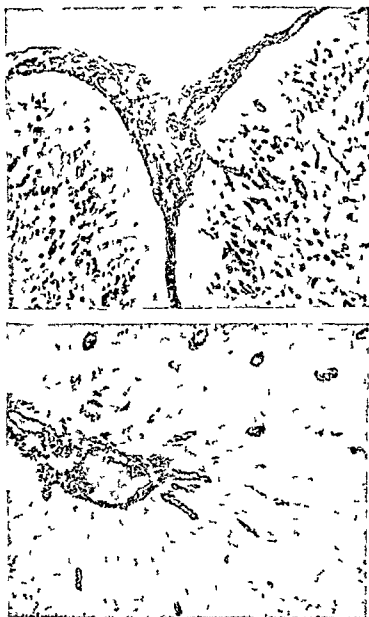
In other cases occluding masses of growth alternate with segments of patent duct or with masses of thrombosed lymph. Permeation frequently extends into the tributaries of the duct, and adjacent thoracic or cervical lymph glands are often affected so that the cancerous duct itself may be difficult to distinguish amidst irregular masses of growth. When the duct is affected throughout its whole length the tumour may project from it into the great veins in the neck. Cancerous occlusion of the thoracic duct is the most frequent cause of chylous ascites, which however, is present in only a minority of cases of such occlusion. Chylo thorax may also be present. These chylous effusions probably result from obstructive ectasia and rupture of tributary lymphatics. (For a valuable review of chylous and pseudo-chylous effusions see Wallis and Scholberg.) The cancerous thoracic duct as a source of metastasis is discussed in the next chapter.

(4) Invasion of veins and capillary blood vessels

Infiltrating tumours frequently invade the walls of small or large veins, penetrate to their lumina and proliferate intravascularly. Certain classes of tumours, e.g. renal carcinoma, are notorious for their behaviour in this way and may extend continuously within large veins for great distances. It is however, important to recognize that venous invasion is not peculiar to any particular class of neoplasms, but is shown in greater or lesser degree by almost all kinds of malignant growths.

(8) Invasion of epithelial cavities

Distension of the major hollow viscera by bulky growths within them and polypoid projection of the growths from orifices, as in the uterus, renal pelvis or alimentary canal, of course does not necessarily imply invasive growth. Extension of malignant tumours within the cavities of main ducts, however, is sometimes an important mode of spread. Thus carcinoma of the kidney or renal pelvis may grow down and distend the ureter and may even enter the bladder, uterine growths may extend back within the Fallopian tubes, nasopharyngeal tumours may grow along the Eustachian tube to the middle ear.



FIGS 39 and 42—Invasion of the perivascular spaces of the brain by a diffuse tumour of the leptomeninges in a child ($\times 40$)

The invasion of minute epithelial spaces sometimes plays an important part in the microscopic extension of tumours. Infiltrating growths in the kidney may

compression of the vessel may result in its obliteration without either tumour invasion of the lumen or the formation of thrombus. Invasion of the lumen however, brings the tumour in contact with the blood stream. Over the invaded area of intima a small thrombus forms (Fig 35). Organization and malignant infiltration of this initial thrombus follow. The thrombus grows steadily until the lumen is occluded, when thrombosis along a section of the vessel takes place.



FIG 36—Section of a large thyroid vein invaded by a metastasis of renal carcinoma in the thyroid. The apparently detached clumps of tumour are cross sections of villiform fringes of growth which projected into the lumen ($\times 60$)

Malignant organization of this column of thrombus follows, and so the process advances section by section along the lumen of the occluded vessel. The relative rates of malignant invasion and organization of thrombus vary. Tumour cells may be found multiplying within unorganized clot. Sometimes masses or strands of naked tumour accompanied by little or no thrombus are seen projecting into the blood stream (Fig 36). Some tumours, e.g. renal carcinoma commonly produce long cylinders of almost pure growth within the vein either occluding the vessel and adhering to its wall or more often leaving a narrow slit like channel carrying some blood flow.

We have been considering examples of tumour invasion of large veins. Even more frequent is microscopic penetration of capillaries and small veins in invaded tissues—a venous and capillary permeation comparable with that of small lymphatics described above (Fig 37). Goldmann was the first worker to appreciate sufficiently the general importance of such permeation of blood vessels in the local extension of tumours and his findings can be confirmed by anyone who

REFERENCES

- Askanazy M (1923) *Zbl allgem Path* 33 (Special Number) 386
- Bland J O W and Russell D S (1938) *J Path Bact* 47, 291
- Carmalt W H (1872) *Virchows Arch* 55 481
- Carrell A and Burrows M S (1911) *J Exper Med* 13 571
- Coman D R (1942 and 1944) *Cancer Res* 1942 2 618 1944 4 625
- COWDRY, E V (1940) Properties of cancer cells *Arch Path* 30 1245 (A valuable review of the physical and chemical properties of tumour cells including a discussion of their invasiveness)
- Cox L B and Cranage M L (1937) *J Path Bact* 45 477
- Dawson E K and Shaw J J M (1937) *Brit J Surg* 25 100
- Ernst P (1905) *Beitr path Anat*, Suppl 7 29
- Fitzwilliams D C L (1924) *Brit J Surg*, 12 650
- Foulds L (1940) *Amer J Cancer*, 39 1
- Fraser J (1927) *Surg Gyn Obst* 45 266
- Fry H and Shattock C E (1926) *Brit J Surg* 14 337
- Fujinami A (1900) *Virchows Arch* 161 115
- Goldmann E (1906) *Lancet* 1 23
- Goldmann E (1907) *Proc Roy Soc Med (Surg Sect 1)*
- GOLDMANN, E (1911) *Studien zur Biologie der bösartigen Neubildungen* Tübingen (Includes a full account of his researches on the spread of tumours by lymphatics and blood vessels)
- Greenough R B (1904) *J Med Res* 13 137
- Grohe F (1865) *Virchows Arch* 32 445
- Handley W S (1906) *Arch Middlesex Hosp* 7, 52
- Handley W S (1907) *Lancet* 1 927
- Handley W S (1922) *Cancer of the Breast* London
- Hanes F M and Lambert R R (1912) *Virchows Arch* 209 12
- Hartz P H and van der Sar A (1942) *Amer J Path* 18 715
- Heidenhain L (1889) *Arch klin Chir* 39 97
- Hertzler A E and Gibson E T (1914) *Ann Surg* 60 88
- Herzog G (1917) *Beitr path Anat* 63 755
- Hoggan G (1878) *Trans Path Soc Lond* 29 384
- Kolodny A (1925) *Arch Surg* 11 690
- Kosa M (1929) *Virchows Arch* 272 166
- Lambert R A (1916) *J Cancer Res* 1 169
- Lewis W H (1936) *Harvey Lectures* p 214
- Leydhecker O (1893) *Virchows Arch* 134 118
- Ludford R J (1934) *Imp Cancer Res Fund Sci Rep*, p 147
- Marchand (1907) *Munch med Wschr* 54 1704
- Polayes S H and Taft H (1931) *Amer J Path* 7 63
- Pulvertaft R J V (1934) *Brit J Surg* 21 701
- Recklinghausen F (1885) *Virchows Arch* 100 503
- Ribbert H (1895) *Virchows Arch* 141 153
- Russell D and Bland J O W (1933) *J Path Bact* 36 273
- Schwedenberg T (1905) *Virchows Arch* 181 295
- Speed K (1925) *Ann Surg* 82 45
- Steinhaus J (1891) *Virchows Arch* 126 533
- STILES, H J (1899) On the dissemination of cancer of the breast *Brit Med J* 1 1452 (An excellent account)
- Stroebe H (1892) *Beitr path Anat* 11 1
- Sutton L A and Mallia W M (1923) *Arch Derm Syph* 8 325
- Vierth K (1895) *Beitr path Anat* 18 515
- Virchow R (1863) *Virchows Arch* 28 237
- Voegtlin C (1937) *Physiol Rev* 17 92
- Vogel L (1891) *Virchows Arch* 125 495

extend along the uriniferous tubules, or in the testis along the seminiferous tubules or in the breast along the ducts. In making this interpretation in the breast great caution is essential, mammary carcinoma is often of multicentric or even diffuse origin and what appears to be extension of tumour within a duct may

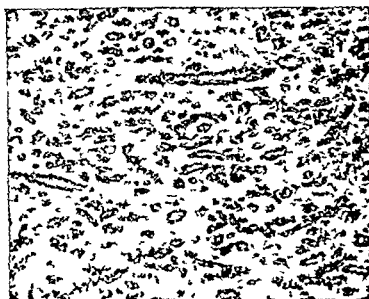


FIG 41 —From same specimen as Figs 39 and 40 ($\times 40$)



FIG 42 —Intra alveolar spread of a metastasis of carcinoma of bladder in lung ($\times 80$)

really be independent malignant change in that duct. A special instance of tumour spread in minute epithelial cavities is seen in lung tissue in which tumours often occupy the air sacs and spread from air sac to air sac *via* the septal pores (Fig 42)

METASTASIS

THE PREFORMED paths along which tumours spread in continuity, as described in the previous chapter, are also the paths through which they metastasize by transport of detached tumour fragments to a distance. These paths are (i) lymph vessels (ii) blood vessels (iii) coelomic spaces, (iv) cerebrospinal spaces, and (v) epithelial cavities. Metastasis by each of these paths will now be considered, further details will be found in my earlier work (Willis, 1934 and 1941)



FIG. 43.—Metastasis of papillary psammo-carcinoma of ovary in a lymph gland. A large afferent lymphatic in the capsule and the subcapsular sinus are occupied by growth which also extends deeper into the gland ($\times 60$)

METASTASIS VIA LYMPH VESSELS

(1) The metastases of carcinomas in lymph glands

One of the most prominent features of the behaviour of carcinomas is their frequent production of secondary growths in regional lymph glands. Most of these growths undoubtedly arise initially from detached tumour emboli carried to the glands in the lymph flow, and not by continuous permeation from the primary growths to the glands. Local recurrences following surgical removal of primary growths of the breast, tongue, lip, vulva, etc., occur either at the site of the primary growth or in the lymph glands, and only rarely at intermediate sites. Many workers have carefully examined the tissues intervening between primary carcinomas and their early lymph nodal metastases, and have failed

- WALDEYER, W (1867 and 1872) Die Entwicklung der Carcinome *Virchows Arch* 1867, 41 470 1872 55 67 (A classical account of the genesis and spread of carcinomas)
- Wallis R L M and Scholberg H A (1911) *Quart J Med* 4 153
- Willis R A (1930) *J Path Bact* 33 501
- WILLIS R A (1934) *The Spread of Tumours in the Human Body* London (Contains fuller details of the subjects of this and the next chapter)
- Willis R A (1941) *Med J Austral* ii 258
- WINKLER K (1878) Ueber die Betheiligung des Lymphgefäß-systems an der Verschleppung bösartiger Geschwulste *Virchows Arch* 151 Suppl 195 (One of the best of the earlier accounts of the spread of tumours by lymphatics and the thoracic duct)
- Wolkoff K and Zinserling W D (1929) *Z Krebsforsch* 28 449
- Wu T T (1936) *J Path Bact* 43 61

glands from various specific groups of carcinomas, see Willis (1934) and the appropriate later chapters of the present work.

TABLE I

LYMPH NODAL METASTASES IN 426 CONSECUTIVE CARCINOMA NECROPSIES

Primary growths (carcinomas)	No of cases	No with metastases in lymph glands
Epidermoid carcinomas of the head and neck - - -	64	51 (80%)
Basal cell carcinoma of skin - - -	5	0
Oesophagus - - -	17	12 (71%)
Stomach - - -	85	76 (89%)
Intestine - - -	65	20 (31%)
Liver - - -	5	5
Biliary tract - - -	13	6
Pancreas - - -	11	8
Breast - - -	45	36 (80%)
Uterus - - -	30	15 (50%)
Ovary - - -	9	6
Prostate - - -	15	9
Kidney parenchyma - - -	10	5
Kidney pelvis - - -	3	3
Bladder - - -	5	2
Lung - - -	27	25 (93%)
Thyroid - - -	6	5
Other sites - - -	11	10
TOTAL - - -	426	294 (69%)

(2) The metastases of non carcinomatous tumours in lymph glands

(a) *Malignant growths of lymphoid tissue*

These as might be expected, frequently produce secondary involvement of multiple glands. This applies to lymphosarcomas, reticulosarcomas, and to their congeners lymphatic leukaemia and Hodgkin's disease. To what extent true embolic metastasis is responsible for the spread of these tumours from gland to gland is uncertain. Metastasis certainly occurs, but direct non embolic spread, and also spread of the neoplastic change itself to further areas of lymphoid tissue also take place.

(b) *Other sarcomas*

Excluding the malignant tumours of lymphoid tissue itself, sarcomatous secondary growths in lymph glands are rare. My series of 500 cancer necropsies (1941) included 18 sarcomas of non lymphoid tissues, and only 3 of these had metastasized in lymph glands. Warren and Meyer studied 237 non lymphoid sarcomas of which 17 (i.e. 7 per cent) were proved to have lymph nodal metastases. These comprised 12 cases of fibrosarcoma and also cases of osteosarcoma, leiomyosarcoma and rhabdomyosarcoma. Other recorded examples of lymph nodal metastases from particular kinds of sarcomas will be referred to in the appropriate later chapters.

to find tumour in the connecting lymphatics (Heidenham, Stiles, Lengemann, Ewing, Willis, Long, Gray). In a series of 40 specimens of carcinoma of the breast surgically removed by the radical method I prepared microscopic sections from blocks of the pectoral muscles and fascia close to the tumours in the breasts, and found cancerous lymphatics in these sites in only 4 cases, in 2 of which there was grossly visible invasion of the muscle beneath the growth. I agree with Gray's conclusions that 'The spread of cancer cells by their growth as cords in the lumina of lymphatics is an unusual phenomenon in cases of operable cancer



FIG. 44.—Metastatic signet ring-cell carcinoma of stomach in peripheral sinus of a lymph gland ($\times 150$)

When it does occur such permeation seems to be generally only of microscopic extent.

For operable cases of cancer embolism is the only important method (of lymphatic spread). In microscopic sections free tumour emboli are sometimes to be found in patent lymphatics (Willis 1934).

The afferent lymphatics of lymph glands open into the peripheral sinuses, in which, therefore, early metastatic deposits are situated (Figs 43, 44). These channels are often to be seen distended by proliferating tumour cells which later extend into the gland. Eventually the entire gland is replaced by tumour tissue which, however, may long remain confined within the intact though distended capsule. Even in advanced cases with multiple glands affected it is likely that embolism from gland to gland is largely responsible. For the affected glands may at first be discrete and unconnected. Later, however, adjacent glands become bound together by tumour occluded lymphatics and infiltrated extra capsular tissues.

The accompanying Table I shows the frequency of lymph nodal metastases in the 426 consecutive necropsies on carcinoma cases reported by me in 1941. For many references to other estimates of the frequency of metastases in lymph

Lymphatic dissemination from the initially affected glands may become extensive, e.g. from the submental or submaxillary glands to many lower cervical, axillary and mediastinal glands. Such extension from gland to gland is almost certainly embolic. Once a particular gland is heavily affected, cancerous occlusion of its main afferent and efferent vessels must lead to diversion of the lymph flow into collateral channels passing to neighbouring unaffected glands. These glands will now receive any emboli coming from the primary source as well as those from the initially affected gland. Every succeeding obstruction must result in further deviations of the lymph flow and further scattering of emboli over a wider and wider area.

A special instance of remote embolic spread from gland to gland is seen in cases of invasion of the cisterna chyli or thoracic duct from cancerous upper lumbar glands, accompanied by discrete metastases in the left supraclavicular glands—Troisier's sign. Most cases with cancerous duct show also cancerous left (and, less frequently right) supraclavicular glands. The mode of infestation of these glands varies. In some cases they are reached by direct extension from a totally cancerous duct but in others the upper parts of the duct are patent and healthy and the cervical deposits are discrete metastases. In such cases we may suppose that tumour emboli borne in the sluggish lymph flow in the upper part of the duct are carried retrogradely into its jugular or other tributaries by respiratory retropulsions of the flow, or possibly that the emboli lodge behind the valves near the termination of the duct and establish small mural lesions whence infestation of the contiguous glands takes place.

Haemic dissemination from cancerous lymph glands is also of frequent occurrence the tumour entering the blood-stream by direct invasion of neighbouring veins or *via* the lymphatic tributaries of veins. Invasion of the main veins of the neck in cases of cranio-cervical carcinoma takes place usually not from the primary growths but from metastatic growths in the cervical lymph glands which lie in close contiguity with the jugular vein and its main tributaries (Willis, 1930, and see below). So also the iliac veins or inferior vena cava are readily invaded by metastatic growths in the pelvic and lumbar glands the pulmonary veins or superior vena cava by deposits in the bronchial and mediastinal glands, and the portal vein or its main tributaries by deposits in mesenteric, peripancreatic or portal glands.

As regards haemic dissemination from lymph glands *via* the lymphatic tributaries of veins the most important instances of this are seen when the cisterna chyli or thoracic duct suffer invasion as described in the previous chapter. This is equivalent to invasion of a large systemic vein and is a potent source of embolic dissemination to the lungs. Most cases with tumour invasion of the thoracic duct show either visible pulmonary metastases or microscopic tumour emboli in the pulmonary arterioles. (For further discussion of the cancerous thoracic duct, see Chapter III of my *Spread of Tumours*.)

(6) Retrograde lymphatic embolism

We have already noted that cancerous replacement of a lymph gland or occlusion of a large lymphatic vessel must result in diversion of the lymph flow into collateral channels and that, as the cancerous affection of lymphatic pathways

(c) *Melanomas*

Melanomas whether of cutaneous or ocular origin frequently produce metastases in lymph glands although haemic dissemination is often the more conspicuous mode of metastasis. In some cases however, lymph nodal deposits appear very early or remain the predominant kind of metastases.

(d) *Embryonic tumours of childhood*

The embryonic tumours of childhood, especially neuroblastomas and nephroblastomas, often produce lymph nodal metastases.

(e) *Malignant teratomas*

Malignant teratomas especially those of the testis, frequently metastasize to regional lymph glands and the metastases may be as complex in structure as the primary growth, or may be simpler.

(3) *Metastases in lymph glands from metastatic tumours in viscera*

Secondary as well as primary tumours produce regional lymphatic metastases. Metastatic growths in the lungs are often accompanied by deposits in the hilar and mediastinal lymph glands, metastases in the portal lymph glands commonly accompany heavy metastatic disease of the liver. Secondary growths in the intestines are often accompanied by involvement of the corresponding mesenteric lymph glands. The distribution of metastatic lesions in many such cases makes it clear that the secondary visceral tumours were indeed the source of those in the neighbouring glands.

(4) *Reactive changes in lymph glands*

There has been some speculation as to whether pre metastatic changes observed in lymph glands have any special significance and whether lymph glands possess any protective or 'barrier' functions against tumours. Neither of these suggestions has any real evidential basis. The pre metastatic changes in glands adjacent to tumour areas consist of simple lymphoid and reticular proliferation and do not differ from the hyperplasias associated with many mild inflammatory states or with the absorption of extravasated blood or of degeneration products. The lymphoid hyperplasias associated with neighbouring tumours are readily explicable as due to mild bacterial infection in superficial growths, to degenerative changes in the tumours, or to blockage of ducts and retention of secretions in glandular organs and no special cancerous noxa need be invoked to explain them.

The supposition that tumour cells are destroyed or their multiplication suppressed in lymph glands is completely at variance with the facts. On the contrary for most carcinomas lymph glands appear to be highly favourable soils. Lymph nodal metastases are often of early appearance and rapid growth and histological study of early metastases fails to disclose any sign of wholesale destruction or arrest of growth of tumour cells (Zehnder, Goldmann 1907. Ewing, Willis 1934).

(5) *Lymph nodal metastases as a source of further metastasis*

Tumour deposits in lymph glands are often the source of further dissemination by the lymph stream or blood stream.

In occasional cases with gross tumour invasion of systemic veins unattached fragments of growth have been found in the post-mortem clots in the right chambers of the heart (Weber Pitt, Griffiths, Geipel, Feinblatt)

The number of tumour emboli circulating in the blood stream must vary greatly from case to case and from time to time. Emboli liberated from small veins are probably few or solitary while gross invasion of large vessels or of the heart chambers no doubt produces plentiful emboli in repeated showers. In cases with widespread tumour deposits and multiple invasions of vessels in many different organs superimposed metastatic cycles must result in great complexity of the process of dissemination and often a high content of tumour particles in the circulating blood (Willis 1930 and 1934)

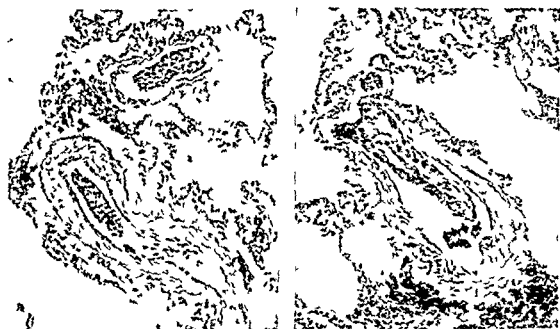


Fig 46 — Tumour-emboli from carcinoma of bladder arrested in pulmonary arterioles ($\times 120$)

Several workers have claimed to have identified free isolated tumour cells in the blood before or after death (Marcus, Jonescu, Pool and Dunlop). Yet granting that some of these may have been genuine tumour cells it is nevertheless certain that metastasis is attributable largely to the dissemination, not of isolated cells but of clumps of cells or masses of thrombus containing cells as already described. In the leukaemias however we see the wholesale circulation of isolated tumour cells.

(3) The three main destinations of blood-borne emboli

Most tumour emboli consisting of fragments of tumour or tumour thrombus, must suffer arrest in the first arterioles or capillaries into which they are carried. With certain exceptions to be considered presently, emboli liberated in systemic veins or in lymphatic tributaries of veins are arrested in the lungs, those liberated in the portal venous system, in the liver and those liberated in the pulmonary veins or left heart chambers in any peripheral organ or tissue to which they are carried in the systemic arterial blood.

extends the available collateral routes must become very devious. Under these circumstances, reversals of flow must commonly occur and retrograde carriage of tumour emboli take place, as first stressed by von Recklinghausen, Vogel and Vierth. Retrograde lymphatic embolism explains such seeming anomalies as the metastasis of carcinomas of the tongue or pharynx to the contra lateral cervical lymph glands, or the occasional metastases of mammary carcinomas to the axillary glands of the opposite side or to the inguinal glands. So also, carcinoma of the stomach or pancreas with deposits in the coeliac and upper lumbar glands is often accompanied by discrete deposits in the lower lumbar, iliac and even inguinal glands—these diminishing in size from above downwards. Doubtless the initial cancerous obstruction in the upper lumbar glands resulted in a retrograde flow of lymph in the lumbar chain of glands which therefore became cancerous step by step in cranio caudal order. Similarly intra thoracic carcinomas with deposits in the mediastinal glands, often exhibit discrete deposits in the abdominal and cervical glands—these diminishing in centrifugal order.

The most extreme alterations in lymph circulation occur when the cisterna chyli and thoracic duct are occluded. The lymph flow in both the retroperitoneal and mediastinal tissues and in the abdominal and thoracic parietes is diverted into numerous collateral channels in many of which there must be reversal of the flow. It is therefore not surprising to find that cancerous disease of the thoracic duct or its main tributaries is usually accompanied by a wide dispersal of tumour deposits in the pelvic, inguinal, cervical and axillary, as well as in the abdominal and thoracic groups of lymph nodes.

Metastasis by retrograde lymphatic embolism is not restricted to lymph glands. Tumour emboli carried retrogradely in large lymphatics may suffer arrest in their peripheral narrower tributaries and give rise to satellite growths around the main one. That this is the mode of development of satellite nodules in the skin around mammary and other growths is clear from the observations of many workers e.g. Winkler, Daus, Haagensen and Stout. Cancerous permeation and occlusion of the deep dermal and fascial lymphatics in the neighbourhood of the main growth first occur—this results in deviations of the lymph flow in a centrifugal often retrograde direction in the surrounding tissues whereby small detached emboli of tumour cells are carried into and arrested in the fine superficial dermal lymphatics of the surrounding skin. Similar local retrograde dissemination in lymphatic channels plays an important part in the extension of some secondary growths in viscera e.g. in widespread lymph vessel carcinosis of the lungs, heart, liver or spleen following cancerous replacement of the regional lymph glands.

(7) Metastatic tumours in lymph glands masquerading as primary ones

Elsewhere (Willis, 1934; Trinca and Willis, 1936) I have recorded many instances of secondary growths in lymph glands having been clinically mistaken for primary lesions. Large secondary growths in the cervical glands may be the first clinically evident result of an otherwise symptomless small primary carcinoma of the tonsil, base of tongue, pharynx, oesophagus or lung or, as a precocious Troisier's sign, of even a gastric or other abdominal carcinoma. Most if not all, so-called "papilliferous lateral aberrant thyroids" are lymph nodal metastases

fibrous organization and it is clear that most of them grow promptly to form metastatic growths

(c) Arrest of tumour emboli in systemic arterioles or capillaries

As might be expected microscopic evidence of tumour embolism is to be found much less frequently in the systemic arterial system than in the lungs or liver. For while the whole of the venous blood traverses the lungs, and the whole of the portal blood traverses the liver, only a fraction of the arterial blood traverses any given organ or tissue. However, recent tumour emboli within arterioles or capillaries have been seen in the heart, by Foot and co workers and by Morris in the kidneys by Eberth Winkler, Busse, Adams Froewis and Willis (1934) in the adrenals by Adams and Robson, in the spleen by Busse, Wegelin, Yokohata, Faulds and Mackay in bone marrow by Piney, and in the thyroid by Rice

(4) Unusual destinations of blood borne emboli

To the foregoing rules as to the usual sites of arrest of blood borne tumour emboli there are five possible or actual exceptions to consider, namely—(a) intracardial implantation, (b) retrograde venous embolism, (c) paradoxical or crossed embolism (d) transpulmonary passage of tumour cells, and (e) transcapillary passage of tumour cells in other organs

(a) Intracardial implantation

Fragments of growth carried in the systemic venous blood rarely become attached to the chordae or cusps of the tricuspid valve or to other parts of the endocardial surfaces of the right heart, and grow into branching or nodular masses within the chambers. This has occurred most frequently with teratomas of the testis (Kanthack and Pigg, Schmeel, Handfield-Jones Morgan), but also with alimentary and other carcinomas (Winter, Kaufmann, Nicholls, Culpepper and von Haam). Left sided endocardial implants from tumour fragments carried in the pulmonary veins are still rarer (Zenker, Kaufmann, Hunter). Branwood and Glazebrook saw a metastatic implant in an atheromatous patch in the root of the aorta

(b) Retrograde venous embolism

Retrograde venous embolism following occlusion of main veins with consequent reversals of flow, accounts for some peculiarly situated metastatic growths. For example, should a carcinoma of the left renal vein, a retrograde flow takes place in the left ovarian or testicular vein and pampiniform plexus, so that tumour emboli may easily be carried caudally and may establish isolated pelvic or spermatic cord metastases. A similar mechanism accounts for fragments of tumours of uterine chorion epitheliomas in the vulva, broad ligament and parts of the pelvis, and probably for some similarly situated secondary emboli from carcinomas of the uterus. It was as von Recklinghausen suggested that some metastatic growths might arise from emboli arrested in the respiratory tract, and those liberally as the result of transient and others systemic retropulsion of blood from a local organ or tissue into the systemic veins. Arnold, Ernst supported this suggestion. von supposed that metastatic

(a) Arrest of emboli in the lungs

The occlusion of microscopic pulmonary arterioles by arrested tumour emboli first clearly described by Andree in 1874, and later by Zenker, Winkler, Schwedenberg Schmidt and others, can easily be verified by anyone who regularly examines sections of the lungs from cases of disseminated tumour (Fig 46)

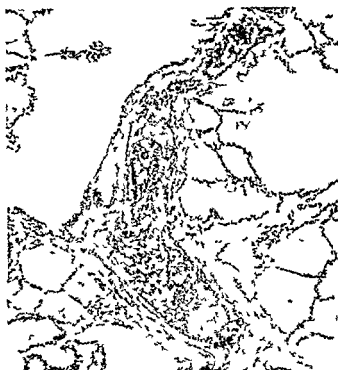


FIG 47—Tumour embolus from carcinoma of duodenum arrested within a pulmonary arteriole ($\times 60$)

These arrested emboli are to be found, not only in lungs containing obvious metastatic growths but also, as Schmidt and many subsequent workers have shown often in lungs devoid of visible metastases. In such cases, the arrested emboli show varying degrees of degeneration and of organization and fibrosis of accompanying thrombus proving their considerable duration yet their contained tumour cells have not proliferated or extended beyond the confines of the occluded arterioles (Fig 47). These sterile or abortive tumour deposits show that metastasis is more than embolism—it includes also the growth of the embolic tumour cells at their site of lodgement.

(b) Arrest of portal emboli in the liver

Arrested tumour emboli in small portal branch veins in the liver have been observed by many workers e.g. Waldeyer (1867) Rolleston Willis (1930 and 1934). These can be found in otherwise unaffected areas of liver as masses of tumour or of tumour and recently formed thrombus occluding veins, usually between 50μ and 500μ in diameter, in the small portal tracts. Unlike tumour emboli in the lungs those in the liver rarely show any signs of degeneration or

the lungs liver and bones, these contained discrete secondary growths in 29, 36 and 14 per cent of all fatal cases of malignant disease. If we exclude the 45 cases of tumours of kinds which never produce remote metastases, then the corresponding percentages are 32, 40 and 15 respectively. Or, if we consider only the 420 cases of carcinoma listed, 30 per cent had metastasized to the lungs, 41 per cent to the liver, and 14 per cent to the bones.

TABLE 41

SITUATIONS OF METASTATIC GROWTHS IN 500 CONSECUTIVE CANCER NECROPSIES

Primary tumours	No. of cases	NUMBER OF CASES WITH METASTASES IN														
		Lungs	Liver	Bones	Adrenals	Kidneys	Brain	Heart	Thyroid	Ovaries	Pancreas	Spleen	Dura	Intestines	Skin	Mucles
Carcinomas																
Epidermoid carcinoma of head and neck	64	19	14	5	5	8	1	4	3	—	2	2	—	1	—	2
Oesophagus	17	3	7	1	—	1	2	1	—	—	1	—	—	—	—	1
Stomach	85	13	39	6	4	—	1	2	1	6	1	—	—	—	—	—
Intestines	65	8	33	1	3	3	1	—	1	2	1	1	1	—	—	—
Biliary tract and liver	18	3	8	2	—	2	—	—	—	1	—	—	—	—	—	—
Pancreas	11	2	8	2	1	—	1	2	1	—	—	—	—	—	—	—
Breast	45	28	22	21	9	7	7	2	8	3	3	4	7	4	—	—
Uterus	30	6	6	1	—	1	—	1	—	1	—	—	—	—	—	—
Ovaries	9	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—
Prostate	15	6	3	3	1	—	—	—	—	—	—	1	2	—	—	—
Kidney (parenchyma)	10	8	5	4	2	4	3	2	3	—	1	—	—	—	1	—
Lung	27	9	15	8	1	4	7	3	2	2	1	—	—	1	—	—
Thyroid	6	6	2	3	2	3	—	2	—	—	2	—	—	—	2	1
Other sites	18	9	10	2	3	2	1	2	—	—	1	3	1	—	—	—
Sarcomas	26	11	2	6	1	—	1	2	—	—	1	—	1	1	2	—
Melanoma	4	3	2	1	3	1	2	—	—	—	—	—	—	1	—	—
Other metastasizing tumours	5	5	3	2	—	2	—	1	1	—	—	2	—	—	—	—
Non metastasizing tumours (brain tumours rodent ulcer etc)	45															
TOTALS	500	147	180	68	45	38	29	24	21	16	15	14	13	9	7	4
Percentages of total	100	29	36	14	9	8	6	5	4	3	3	3	3	2	1	1

(6) Tissues as soils for blood borne metastases

Elsewhere (1934) I have discussed in some detail the many peculiarities of distribution of metastatic tumours and the reasons for rejecting Ewing's opinion that "the mechanism of the circulation will doubtless explain most of these peculiarities". Stephen Paget (1889) was one of the first to be struck by the discrepancies in the relative frequencies of metastatic growths in various organs and by the peculiarly selective distribution of the metastases of tumours of certain kinds and to liken tumour emboli to 'seeds' falling in 'soils' of different degrees of fertility. Many later workers have expressed similar views, and have concluded that different chemical or other factors in various tissues must determine whether or not arrested tumour particles shall germinate to produce secondary growths.

We have already encountered direct evidence of the truth of the "seed soil" relationship in tumour metastasis. We have seen that some tumour emboli arrested in the lungs fail to grow there, but remain infertile within the occluded

growths in the spleen could arise by retrograde carriage of tumour emboli from the liver *via* the portal and splenic veins. Elsewhere (1934) I have given reasons for rejecting this view. all alleged instances of tumour embolism in unobstructed large veins are open to other and preferable interpretations

(c) *Paradoxical or crossed embolism*

Paradoxical or crossed embolism i.e. systemic arterial embolism by particles liberated in systemic veins but avoiding the lungs by traversing a patent foramen ovale must be admitted as a theoretical possibility but is certainly a rare and unimportant event in the dissemination of tumours. Thompson and Evans, reviewing the whole subject, rightly concluded that claims for tumour metastasis by crossed embolism can be sustained only when careful microscopic study has proved the lungs to be free of growth, and none of the reported cases fulfils this requirement.

(d) *Transpulmonary passage of isolated tumour cells*

This has often been assumed to explain cases of tumour dissemination in systemic viscera without visible affection of the lungs. As with claims for paradoxical embolism, however, so also those for unarrested passage of cells through the pulmonary capillaries can only be entertained when painstaking study has proved the absence of microscopic metastases and of arrested tumour emboli in the pulmonary arterioles, and such proof has not been advanced. In view of what was said above regarding the usual sizes of blood borne tumour emboli, it is certain that wide tumour dissemination with seemingly unaffected lungs is much more often to be attributed to abortive tumour embolism in these organs than to unarrested traversal of them by single tumour cells.

(e) *Traversal of systemic capillaries by tumour cells*

It has been suggested that traversal of systemic capillaries by tumour cells accounts for the relative immunity of certain contractile organs such as muscles, myocardium, visceral muscle coats and the spleen, from tumour metastasis, the implication being that isolated tumour cells are massaged through the capillary channels into the veins. However, since many tumour cells are too large to traverse capillaries and since most tumour emboli consist not of single cells but of considerable aggregates, it is certain that the vast majority of such emboli must suffer arrest in the arterioles or capillaries of any tissue. What has just been said of supposed transcappillary passage in the lungs applies *mutatis mutandis* to that in other tissues.

(5) *The frequency of blood borne metastases in various sites*

For a detailed account of the pathology of secondary tumours in particular organs, the reader must consult Part II of my 1934 work. Table II shows the frequency of true metastatic tumours in various sites in 500 consecutive necropsies on cases of malignant disease (Willis 1941). all of the growths listed except those in the ovaries were discrete blood borne metastases, cases of direct invasion of the organs being excluded. The three most frequent sites of metastases were

The precise chemical, enzymic or other factors involved in the successful growth or failure of transported tumour cells are still unknown. But light will be shed on the problem by future researches in the metabolism of normal tissues and of tumours, by tissue culture studies, and by the prosecution of studies like those suggested by Burrows in his excellent book, "Some Factors in the Localization of Disease in the Body."

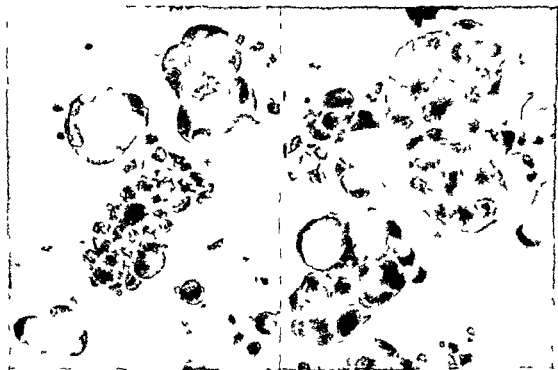


FIG. 48.—Clumps of signet ring tumour cells in pleural fluid from carcinoma of lung ($\times 400$)

TRANSCOELOMIC METASTASIS

In the development of widespread carcinomatosis of serous membranes liberation of detached tumour cells or larger fragments into the serous cavity and implantation of these on other parts of its surfaces play the main part, and permeation and metastasis in the subserous lymphatic plexuses only a subsidiary part. Useful accounts include those of Fiddes and McLean, Sampson, and Willis (1934).

(1) The entry of tumours into coelomic cavities

The site of entry of tumour cells into a serous cavity is often plainly apparent, as in many cases of papilliferous ovarian growths, or of gastric or intestinal carcinomas especially those of the gelatinous type. Tumours of the uterus, bladder, prostate, pancreas or kidney seldom disseminate in the peritoneal cavity unless the primary growths or their metastases in lymph glands have extended to the peritoneal surface. Pleural carcinomatosis follows primary or secondary growths in the lung only when these have involved the pleural surfaces. Pericardial

arterioles and undergo degeneration and fibrous organization. In the liver on the contrary, abortive tumour emboli are rarely or never encountered. Liver tissue is clearly a favourable soil for the germination of most kinds of tumour emboli, while lung tissue is not infrequently an unfavourable soil. Confirmation of this is afforded by study of the mitotic activity of metastatic tumours. Metastases of a particular tumour in different situations show great differences of mitosis, and the mitotic activity of hepatic metastases usually exceeds that of the primary growth and of secondary growths elsewhere, sometimes five fold or ten fold (Willis, 1932).

The absence of microscopic evidence of abortive tumour embolism in the liver and the high mitotic activity of hepatic metastatic growths no less than the great frequency, size and number of such growths, show clearly that hepatic tissue is a fertile soil for tumour growth. In 1907 Bland Sutton suggested that this might be due to the high nutritive qualities of the portal blood and the abundance of stored glycogen in the liver. Later (1934), in the light of Warburg's work, I amplified this idea by suggesting that the poor oxygenation of the liver as well as its high carbohydrate content might favour tumour growth in it. Haddow (1934), however, reviewing this question, thought it not unlikely that a more specific mechanism is involved and that the liver is the source of a growth promoting substance of paramount importance in the division of both normal and malignant cells.

In contrast with the liver, skeletal muscular tissue is clearly an unfavourable soil for the germination of disseminated tumours. In spite of a very large aggregate blood supply which must bring to the muscles a correspondingly large share of the tumour emboli distributed by the arterial blood, this tissue is a rare site of metastatic growths, as indeed of metastatic lesions generally, including infections. There is nothing peculiar in the arteriolar and capillary circulation in muscle to account for this relative immunity; we are obliged to seek the explanation in the peculiar metabolism of muscular tissue, in which it may be noted lactic acid—also an important product of many tumour cells—plays a prominent part.

The contrasting properties of various tissues as soils for embolic tumour cells must depend largely on metabolic differences relevant to the requirements of these cells. Doubtless different kinds of tumours display different metastatic distributions because they have different metabolic requirements. Tissue-culture work shows the importance of the chemical environment for the survival and growth of cells of different kinds. Food substances, oxygen supply, hydrogen ion concentration and special growth promoting substances (trephones) all play a part in influencing the vigour of cultures. The condition of tumour cells in detached emboli or embedded in unorganized thrombus resembles that of a tissue culture: the nutritive and other requirements of the cells must be supplied by simple diffusion. Hence just as in artificial cultures the success or failure of embolically transplanted tumour fragments must depend on the chemical suitability or otherwise of their new environment. The critical period for disseminated tumour cells must be that immediately following their embolic lodgement before they have achieved any stromal connections with the surrounding host tissues, and while they are wholly dependent for their nutrition on diffusion from these tissues. Adverse chemical factors at this stage must be a major cause of abortive tumour embolism.

cells in ascitic fluid during life. The healthy appearance of many of the cells in cancerous effusions, and the presence of mitotic figures in them (Fig 49), accord with their ready powers of establishing metastatic implants. Some animal tumours which grow prolifically in the peritoneal cavity are easily transferable to other animals by intraperitoneal inoculations with either minced tumour tissue or ascitic fluid containing tumour cells.

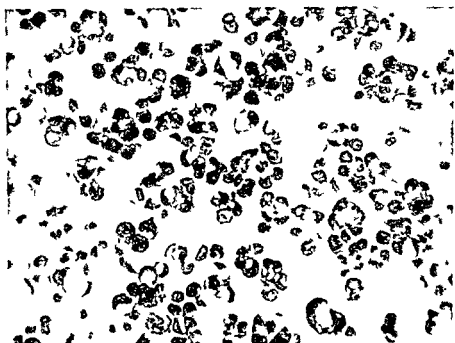


Fig 50—A heavy deposit of signet ring carcinoma cells in ascitic fluid from a woman aged 45 with palpable abdominal tumours possibly of gastric origin ($\times 300$)

(3) The histology of implantation

Misumi, Sampson and others have described the implantation and early growth of transcoelomic metastases. Following deposition of a clump of tumour cells on the serous surface, mild reactionary changes take place in the subjacent tissues, and a fibrinous exudate appears on the surface around the tumour cells. Organization of the fibrin follows: proliferating vessels and fibroblasts grow into it from the subserous tissues and convert it into a true stroma for the proliferating tumour cells. They begin to infiltrate the underlying tissues and the young metastasis is established. Sometimes the tumour cells grow over the serous surface in characteristic epithelial arrangement, and if they are mucus secreting cells, they often discharge their secretion directly into the serous cavity. (For illustrations of these changes see Sampson's excellent papers.)

(4) The distribution of transcoelomic metastases

(a) *In the peritoneal cavity*

Doubtless owing to the effect of gravity in the usual erect or semi recumbent postures, the earliest or most abundant tumour deposits are often found in the pelvis, especially in the recto vesical or recto uterine pouch. Another frequent

implants are rarely seen unless the parietal pericardium has suffered obvious invasion from without

In occasional cases of nodular sowing in a serous cavity, no obvious source of this is to be found, and we must admit that the infestation may have taken place from inconspicuous lymphatic extensions of growth. This is not surprising for even a small single inoculum of tumour cells might suffice to initiate wide spread coelomic dissemination the initial implant yielding successive secondary implants. In breast carcinoma, Handley (1922) attributed special importance to inconspicuous extensions of growth through the parietes from the deep fascial lymphatic plexus to the subserous plexuses and believed this to be the usual route of extension to both the serous cavities and the viscera. Others however, including Cheatle and Cutler Gray, and myself, have failed to find any evidence in favour of this view



FIG 49—Clumps of tumour cells in pleural fluid from woman aged 60 with presumed carcinoma of lung. M = a cell in mitosis. V = a vesicle of tumour cells ($\times 300$)

(2) Free tumour particles in serous cavities

Many workers have seen free tumour cells or cell aggregates in the effusions accompanying peritoneal or pleural carcinomatosis (Beneke Pusinelli and Geipel Gwyn Ssobolew Josefson Jacobsthal Kaufmann Zemansky Sampson, Karp, Graham, and de Vries). Josefson was the first to search for tumour fragments in stained sections of the centrifuged deposit a technique which was used also by Zemansky, Karp and Graham and which facilitates identification of tumour cells in fully one half of the cases of effusions due to tumours (Figs 48 50). The tumour cells may show mitotic figures. Glandular tumours are often recognizable by the presence of signet ring cells or of complete glandular acini or vesicles. Free floating carcinomatous vesicles first described by Beneke have also been recorded by Graham and de Vries. Hickling described the vital staining of tumour

(b) Adhesions

Adhesions frequently accompany tumours in the serous cavities. They may become very extensive, binding the viscera into an inseparable scirrhus mass in which it is impossible to distinguish transcoelomic dissemination from diffuse infiltration of tissues. Carcinomas of the stomach and breast are the most prone to produce diffuse adhesive disease of this kind.

(c) Accumulation of mucus

In the serous cavity accumulation of mucus often results from massive or disseminated mucoid adenocarcinomas ("colloid cancer"), good accounts of which were given by McCrae and Coplin, and Roth. When carcinomatous tumours discharge large quantities of mucus into the peritoneal cavity, the result is identical with that of "pseudomyxoma peritonei", a term first applied by Werth (1884) to massive gelatinous accumulations resulting from perforated pseudomucinous cystadenomas of the ovary.

(6) Secondary tumours in serous cavities masquerading as primary ones

Clinical misdiagnoses may be caused by the coelomic metastases of otherwise symptomless primary growths elsewhere. Many cases have occurred in which the pelvic deposits of gastric or other abdominal carcinomas have been mistaken for primary carcinomas of the rectum (Toyosumi, Dann, Wakasugi, Boas, Anson). Even mammary carcinoma may be overlooked while producing its main symptoms by its coelomic deposits, this had happened in one of my necropsy cases, in which peritoneal metastases had led to a diagnosis of "cholecystitis". The frequent simulation of primary by secondary growths in the ovaries is well known.

Pathological misdiagnoses of primary 'endotheliomas' or "mesotheliomas" of serous membranes have frequently been made in cases of secondary disease from unrecognized primary growths elsewhere. In 1934 I reviewed many reported cases of supposedly primary neoplasms of serous membranes and concluded that most, if not all of them were only examples of serosal disease secondary to undiscovered tumours, usually in neighbouring viscera. My perusal of the more recent literature and my own later experience have confirmed that opinion. I find accounts like those of Wells (1935) and of Yoshida (1937), of serosal 'papillomatosis' incomplete and unconvincing. Wells failed to examine microscopically an enlarged prostate, or to mention the pancreas and thyroid, or to indicate how thorough his examination of the bronchi and alimentary tract had been, and Yoshida's report suffers from similar omissions. Gomori's diagnosis (1936) of "peritoneal mesothelioma" made from a biopsy specimen removed during laparotomy on a man of 49, who had had gastric symptoms for 9 months and in whom a skiagram had shown a pre-pyloric filling defect diagnosed as carcinoma needs no further comment. None of Geschickter's large collection (1936) of supposed "mesothelial tumours" of serous membranes is adequately reported. In Fahr's 7 cases (1935) of "fibro-endotheliosis" of the pleura the necropsy accounts are incomplete, and the figures more than confirm Fahr's opinion that the tumours "resembled" carcinomas. Scheidegger (1935) properly identified as carcinomas 4 tumours which involved the pleura diffusely, but his suggestion

site is along the attachment of the mesentery to the small intestine, probably because the many small recesses alongside the entering mesenteric vessels favour the lodgement of tumour particles. The omentum and epiploic appendices are often heavily infested, and in some cases especially of upper abdominal carcinomas, the most numerous nodules are found on the undersurface of the diaphragm, particularly on the right side. No part of the peritoneal surfaces is exempt and in advanced disease heavy confluent tumour deposits are almost universally present.

Transperitoneal deposits may affect hernial sacs, as described by Rolleston and by Satke and Salzer, and as in the following four personally observed examples

- (i) Male 47. Anaplastic carcinoma of liver. metastases in fundus of inguinal hernial sac found at necropsy (Willis 1934)
- (ii) Male 68. Squamous-cell carcinoma of tonsil with widespread metastases. contents of bilateral inguinal herniae found at necropsy to be infiltrated by growth (Willis 1941)
- (iii) Male 46. At operation for repair of a long standing inguinal hernia which had recently become painful sac was found to have nodular thickened walls which microscopically showed spheroidal-cell carcinoma. Recent indigestion suggested gastric carcinoma (Trinca and Willis)
- (iv) Male 62. Recent discomfort had been noticed in long standing bilateral inguinal herniae. Patient was admitted urgently to hospital because of an attack of vomiting thought to be due to obstruction but herniae were reducible. Laparotomy disclosed carcinoma of stomach with peritoneal metastases. Necropsy verified this and showed deposits of growth in both hernial sacs.

Transcoelomic metastasis is responsible for most secondary growths in the ovaries which are discussed in relevant chapters of Part II

(b) *In the pleural cavity*

In the pleural cavity transplanted tumour nodules may be found in all parts but are often most abundant in the costo phrenic recesses on the surface of the diaphragm or along the paravertebral gutters.

(c) *In the pericardial cavity*

In the pericardial cavity discrete nodular transplants are not common and they must be distinguished from nodules springing from secondary growths permeating the epicardial lymphatics.

(5) Results of secondary tumours of serous membranes

(a) *Effusions*

Effusions serous or haemorrhagic are frequent resulting partly from cancerous occlusion of lymphatics and veins and partly from irritative exudation evoked by the growths. The frequent admixture of blood in cancerous effusions is due largely to obstruction and damage of small veins. A persistent haemorrhagic effusion always strongly suggests malignant disease. Chylous effusions do not result from serosal carcinosis *per se* but from obstruction and ectasia of the thoracic duct or its main tributaries. Pseudochylous effusions are due merely to admixture of fatty degeneration products of tumours with coelomic effusions.

It is probable also that blood-borne metastatic growths in the dura mater or cranial bones may sometimes be the source of meningeal dissemination

Not a few cases have been reported in which disseminated carcinomatosis of the meninges has been unaccompanied by any demonstrable metastatic growths in the brain, as in 14 cases reviewed by Hoffmann and others reviewed by me (1934). Several reporters of such cases, notably Knerim, and Alpers and Smith, have attributed the meningeal infestation to invasion of the spinal theca from without *via* nerve sheaths and the spinal nerve roots. While this sequence must be admitted as quite possible, it is also possible in such cases that small undischarged blood borne metastases in the brain, choroid plexus or meninges themselves may have been the source of the meningeal dissemination

(2) Tumour cells in cerebrospinal fluid

As far as I know, glioma cells have not been identified in cerebrospinal fluid during life. The most likely to be found would be those of medulloblastomas, but these cells might be difficult to distinguish from lymphocytes. Tumour cells which have been identified in the fluid include those of many kinds of carcinoma (references, Willis 1934, and Duncan's case), a thymic tumour in a child (Danisch and Nedelmann), a round cell ocular sarcoma (Panton), and probably a pituitary adenoma (Cairns and Russell). Mitotic figures in tumour cells in cerebrospinal fluid were seen by Panton, Humbert and Alexieff.

(3) The sites and appearances of fluid borne metastases

(a) *In the leptomeninges*

As might be expected, meningeal implants are usually most abundant in the basal and spinal regions, and in the latter the heaviest deposits are often around the cauda equina. The posterior surface of the cord is more affected than the anterior. The spinal or cranial nerve roots may show prominent deposits. The deposits may appear as small scattered nodules or plaques, and may be mistaken for tubercles, as in my case referred to above. More often they are rather diffuse, varying in naked eye appearance from slight indefinite thickenings of the pia arachnoid only to be identified microscopically, to a massive white sheath completely enveloping the cord or brain surfaces, and sometimes filling the thecal space. These massive diffuse investments are most common with medulloblastoma. Their misdiagnosis as 'sarcomatosis' of the meninges is discussed in my earlier work.

(b) *Ventricular implants*

Ventricular implants usually in the form of discrete scattered nodular growths, have been seen from oligodendroglioma (Martin), papillary growths of the choroid plexus (van Wagenen, Cairns and Russell), metastatic carcinoma (Barnes) and pineal teratoma (my Case No. II Chapter 61).

METASTASIS BY IMPLANTATION ON EPITHELIAL SURFACES

Medical records contain many supposed instances of metastasis by transplantation of detached tumour cells on epithelial surfaces. But there are strong grounds for rejecting this interpretation in most cases. Not only does successful

that they may have arisen from ectopic epithelium is unnecessary. The "localized pleural mesothelioma" reported by Stout and Murray (1942) is unacceptable on two grounds, the large tumour involved the left main bronchus and had a structure quite compatible with bronchial carcinoma and the uterus also contained a malignant growth of which the lung tumour may possibly have been a metastasis. The tumour reported by Dick as an "endothelioma of the pericardium" involved the root of the lung, and the figures show adenocarcinoma.

The only tumour which I myself have ever ventured to suggest might be a primary one of a serous membrane was in a case reported in 1938. This was a polypoid growth inside a large surgically removed hydrocele sac. Subsequent necropsy showed this to have been a metastasis from a small unsuspected bronchial carcinoma.

METASTASIS IN CEREBROSPINAL CAVITIES

Any malignant tumour, primary or secondary in the brain or meninges encroaching on any surface bathed by cerebrospinal fluid may liberate tumour cells or fragments into the fluid and these may implant themselves to produce metastases on near or distant surfaces of the meninges or ventricles. Such cerebrospinal metastasis is closely similar to transcoelomic metastasis in a serous cavity containing an effusion. (For detailed discussion see Willis 1934.)

(1) The entry of tumour cells into cerebrospinal fluid

The dissemination of gliomas by way of the cerebrospinal fluid was discussed particularly by Cairns and Russell. Of the gliomas the most prone to disseminate is medulloblastoma, the usual situation of which in the roof of the fourth ventricle gives it immediate access to the cisterna magna via the foramina of Luschka and Magendie. So also papillary growths of the choroid plexus frequently produce metastases in the basal and spinal meninges. Several instances of cerebrospinal metastasis from ependymal gliomas of the fourth ventricle have been reported. Cerebral gliomas which have produced meningeal metastases usually show gross invasion of the ventricular system or of the surface of the brain as in the case of astrocytoma of the thalamus described by Russell and Cairns. Retinoblastomas invading the optic nerves and brain may metastasize by the cerebrospinal fluid. In a case of pineal teratoma which partly filled the third ventricle (Case No. II Chapter 61) I saw a discrete implant in the lateral ventricle and Berblinger (1925) described a pineal tumour which had invaded the quadrigeminal bodies and cerebellum and had metastasized to the meninges of the cauda equina.

When metastatic growths in the central nervous system disseminate in the meninges by way of the cerebrospinal fluid the site of invasion of the cerebrospinal spaces by the growth is often clear (see Hoffmann, Heinemann, Humbert and AlexiEFF, Willis 1934). The sequence of events is particularly clear in those cases in which metastatic growths involving the ventricular walls or in the choroid plexus are accompanied by widespread deposits in the cranial and spinal leptomeninges as in those described by Weller, Ginsberg, Putschner, Fried, Danisch and Nedelmann and in a case of my own (1934). That the extension of metastatic growths to the pial surfaces of the brain may also initiate cerebrospinal dissemination is shown by other reported cases e.g. that of Duncan

However, there have been at least three recorded cases in which intrabronchial metastasis appears clearly to have occurred. In Hitz and Oesterlin's case, a large papillary growth in the larynx of a child was accompanied by multiple intrabronchial deposits in the lungs. In the case described by Vorzimer and Perla, a large maxillary adamantinoma had invaded the nasal cavity and nasopharynx and had been operated on several times under general anaesthesia. necropsy revealed a large tumour cast growing in and distending the bronchi of the lower lobe of the right lung, and there were no other metastases. In von Zalka's case a squamous cell carcinoma of the larynx was accompanied by a metastatic nodule in the mucosa of the right main bronchus and by multiple small intrabronchial growths in the lungs, no lymph nodal deposits were found but there were some small metastases in the kidneys. Although von Zalka admitted the objections he believed, with good reason, I think, that aerial metastasis best explained the findings.

Since aerial metastasis can sometimes take place from the upper to the lower parts of the respiratory tract we must admit the possibility that tumours in the lungs may sometimes disseminate within the lungs themselves by the aerial route. Proof of this would be well nigh impossible to obtain in human beings but animal experiments might be designed to demonstrate the inoculability of the lungs to tumours by way of the air passages. Indeed, Furth (1946) has carried out some experiments of this kind, which show that it is possible to produce tumours in the lungs of mice by the intranasal insufflation of leukaemic or carcinomatous cells.

(4) Implant metastasis in the female genital tract

In this territory local metastasis by lymphatic and venous channels is so frequent, that proof of the occurrence of surface implantation is difficult to attain. There is no doubt, however, that implantation of tumours does take place in the tubal mucosa and in the endometrium. More or less convincing instances of the intra tubal implantation of fragments of abdominal or uterine carcinomas include those of Glendinning, Kaufmann, Kundrat, Werner, Offutt and Sampson (1924 and 1938). In particular, Sampson's 1938 paper fully demonstrates the occurrence of intra tubal metastases from ovarian carcinomas. Although complete proof is lacking I think also that the work of Taussig, Burkhard, Novak and Offutt leaves little room for doubt that ovarian or Fallopian tumours can produce endometrial implants.

On the other hand supposed instances of implant metastases of uterine tumours in the vagina or vulva are unconvincing. Undoubtedly, as Kaufmann, Milner and others have shown these are all attributable to submucous extensions or local metastases by way of lymphatics or veins.

(5) Implant metastasis in the urinary tract

Papillary growths of the renal pelvis or ureter, accompanied by smaller secondary growths in the lower part of the ureter or bladder are well known. Are these 'secondary' growths due to surface implantation, to intra mural lymphatic extensions or to multicentric primary origin? In most cases they are certainly not due to lymphatic extension for such multiplicity is seen with

transplantation on such surfaces as the skin or the alimentary mucosa appear most improbable on general grounds but many supposed instances of metastasis by transplantation are clearly susceptible of other and preferable explanations—either as multiple primary growths or metastases by other well known routes (For critical discussions, see the papers of Schimmelbusch, Bucher, Kaufmann, Milner, Borrmann and Chapter VI of my 1934 work)

(1) Contact cancers of skin and other squamous stratified epithelia

Contact carcinomas of opposed epithelial surfaces are not uncommon in the skin, vulva lips tongue and cheek, larynx and conjunctiva. There is little doubt that multiple tumour formation in areas of similarly prepared epithelium accounts for most of these. In all of these regions we encounter multiple growths not in contact but clearly the result of multifocal neoplasia in a susceptible epithelial field as described in Chapter 7. The susceptibility of the field may consist of some well recognized pre-cancerous state such as leucoplakia in the vulva, or syphilitic disease in the oral cavity. The precise opposition of a contact cancer developing in such circumstances may well be determined by the mechanical and chemical irritation inflicted by the initial growth on the opposed already pre-cancerous surface. Infrequently contact cancers may be due to direct subepithelial extensions of the initial growth. Rare instances of supposed tumour inoculation of parts of the skin remote from the initial growth may be dismissed as pure coincidences. So also may alleged cases of surface transfer of tumour from one person to another.

(2) Implant metastasis in the alimentary tract

The inherent improbability of tissue grafts taking successfully on intact surfaces bathed by digestive juices and mucus and rich in bacteria, justifies the greatest stringency in judging alleged instances of tumour implantation in the alimentary canal. Critical examination of such cases shows that the supposed implants are to be attributed either to multiple primary tumour formation or to transcoelomic or vascular metastasis. Supposed implants in the oesophagus or stomach are usually due to outcropping from submucosal lymphatic extensions of the initial growth (Zahn, Bucher, Milner, Borrmann) but multicentric origin is sometimes responsible. Multiple carcinomas of the large intestine are now so well known, that I doubt whether anyone would seriously advance the implantation hypothesis to explain them. Teacher (1930) was I think the last to support this hypothesis for alimentary tumours. In a case of carcinoma of the gall bladder he attributed the multiple growths which were present in the mucosa of the small intestine to implantation of particles of growth which he supposed had passed down the bile duct into the bowel.

(3) Implant metastasis in the respiratory tract

In the great majority of cases in which secondary growths in the lungs from tumours in the upper respiratory tract have been attributed to intrabronchial metastasis this suggestion can readily be dismissed. The lung metastases arrived by the usual vascular routes.

- Dann W (1910) *Dtsch Z Chir* 106 307
- Daus S (1907) *Virchows Arch* 190 196
- Dick J C (1938) *J Path Bact* 47 43
- Duncan C A (1944) *Med J Austral* 11 541
- Eberth C J (1873) *Virchows Arch* 58 58
- Ernst P (1898) *Virchows Arch* 151 69
- Ewing J (1940) *Neoplastic Diseases* Philadelphia
- Fahr T (1935) *Virchows Arch* 295 502
- Faulds J S and Mackay W (1927) *Lancet* 11 1334
- Feinblut H M (1926) *Arch Int Med* 38 469
- Fiddes J and McLean J A (1929) *Med J Austral* 1 455
- Foot N C, Carter B N and Flipse M J (1924) *Amer J Med Sci*, 167, 76
- Fried B M (1925) *Arch Int Med* 35 1
- Froewis E (1930) *Wien klin Wschr* 43 1227
- Furth J (1946) *Amer J Path* 22 1101
- Geipel P (1904) *Munch med Wschr* 51 2207
- Geschickter C F (1936) *Amer J Cancer* 26 378
- Ginsberg S (1921) *Klin Mbl Augenheilk* 67 232
- Glendinning B (1910) *J Obst Gyn* 17 24
- Goldmann E (See References Chapter 9)
- Gomori G (1936) *Amer J Surg* 33 150
- Graham G S (1933) *Amer J Path* 9 701
- GRAY, J H (1939) The relation of lymphatic vessels to the spread of cancer *Brit J Surg*, 26 462
- Griffiths J (1888) *Trans Path Soc Lond* 39 311
- Gwyn N B (1904) *Amer J Med Sci* 127 592
- Haagensen C D and Stout A P (1943) *Ann Surg* 118 1
- Haddow A (1934) *Amer J Cancer* 22 308
- Handfield Jones R M (1926) *Brit J Surg* 13 606
- Handley W S (1922) *Cancer of the Breast* London
- Heidenhain L (1889) *Arch klin Chir* 39 97
- Heinemann J (1911) *Virchows Arch* 205 418
- Hitz H B and Oesterlin E (1932) *Amer J Path* 8 333
- Hodlmoser (1904) *Z Heilk* 25 109
- Hofmann H (1909) *Z Krebsforsch* 7 655
- Humbert G and Alexieff W (1913) *Rev Med* 33 921
- Hunter J B *Proc Roy Soc Med* 15 (Sect Obst) 22
- Jacobsthal E (1921) *Verh Dtsch path Ges* 18 182
- Josefson A (1916) *Z klin Med* 82 331
- Jonescu P (1931) *Z Krebsforsch* 33 264
- Judd E S and Scholl A J (1924) *J Amer Med Assoc* 82 75
- Kantrick A A and Pigg T S (1897) *Trans Path Soc Lond* 48 139
- Kantrick A A and Pigg T S (1898) *J Path Bact* 5 78
- Karp H (1932) *Z Krebsforsch* 36 579
- Kaufmann E (1898) *Virchows Arch* 154 1
- Kaufmann E (1929) *Pathology* (translation by Reimann) Philadel
- Kricmar G (1903) *Butr path Anat* 44 409
- Kundrat R (1906) *Arch Gynak* 80 384
- Lengemann (1902) *Arch klin Chir* 68 387
- Long E R (1935) *Amer J Cancer* 23 75
- Marcus H (1917) *Z Krebsforsch* 16 217
- Martin J P (1931) *Brain* 54 330
- McCrae T and Coplin W (1916) *Amer* 475
- MILNER R (1904) *Giebt es Impf Cc* klin Ch
- excellent critical review)
- Misumi J (1909) *Virchows Arch* 196 31
- Morgan J R E (1934) *J Lab Clin Med*

tumours of relatively benign type with no evidence of invasive spread and even in frankly malignant cases the small 'secondary' growths are often restricted to the mucosal surface and there is no sign of any cancerous lymphatics in the tissues beneath them. Multiple tumour formation in the urinary epithelium undoubtedly occurs very frequently (see Chapter 28). Is it possible then that all supposed implant tumours are multiple formations in a field of epithelium everywhere exposed to the same carcinogenic stimuli? There are three objections to this view. (a) in many cases in which implantation is suggested there may be long reaches of apparently normal mucosa between the primary and 'secondary' growths, with no evidence of any general inflammation or hyperplasia such as are seen in cases of aniline cancer or bilharzial cancer. (b) 'implant' tumours usually arise not fortuitously in any other parts of the urinary epithelium, but at points caudal to the main tumour in the corresponding ureter or in the bladder and (c) at least one carefully studied case is recorded in which it seems clear that an extra urinary growth an adenocarcinoma of the rectum, had invaded the ureter and had produced implant metastases in the calices of the hydronephrotic kidney (Boger). If an extrinsic tumour can implant itself in the urinary passages the same capacity to a higher degree must be admitted for indigenous tumours. From the available evidence then we must concede that metastasis by implantation may occur in the urinary passages but it will often be difficult or impossible to distinguish between this and multiple formation. Experiments might be performed to ascertain the inoculability of the urinary surfaces to tumours in animals.

REFERENCES

- Adams F D (1921) *Arch Int Med* 27 175
 Alpers B J and Smith O N (1938) *Amer J Cancer* 32 361
 ANDRIE C (1874) Beitrag zur Lehre von der Entstehung des Geschwulstmetastasen auf embolischem Wege *Virchows Arch* 61 383 (A classical account)
 Anson C E H (1927) *Lancet* i 704
 Arnold J (1891) *Virchows Arch* 124 385
 Barnes S (1905) *Brain* 28 30
 Beneke R (1899) *Dtsch Arch klin Med* 64 237
 Berblinger W (1925) *Z ges Neurol u Psych* 95 741
 Boas J (1911) *Dtsch med Wschr* 37 2277
 Boger A (1928) *Beitr path Anat* 80 640
 BORRMANN R (1910) Die Beurteilung multipler Karzinome im Digestionstraktus mit besonderer Berücksichtigung des Einbruchs karcinomatöser Metastasen unter Vortäuschung primärer Tumoren *Beitr path Anat* 48 576 (A valuable critical review of supposed implant metastasis in the alimentary canal)
 Branwood A W and Glazebrook A J (1946) *J Path Bact* 58 286
 Brown C E and Warren S (1938) *Surg Gyn Obst* 66 611
 Bucher R (1893) *Beitr path Anat* 14 71
 Burekhard G (1924) *Z Geburts Gynak* 87 350
 BURROWS H (1932) *Some Factors in the Localisation of Disease in the Body* London
 Busse O (1903) *Virchows Arch* 174 207
 CAIRNS H and RUSSELL D (1931) Intracranial and spinal metastases in glioma of the brain *Brain* 54 377
 Cheate L and Cutler M (1931) *Tumours of the Breast* London
 Culppepper A L and von Haam E (1934) *Amer J Cancer* 21 355
 Danisch F and Nodelmann E (1928) *Virchows Arch* 268 492

sometimes quoted seriously and approvingly. Whatever may have been the influence of Cohnheim's and Ribbert's speculations in the evolution of our knowledge of the nature and origin of tumours, it is time that modern pathologists should cease to regard them as of more than historical interest.

THE CHRONIC IRRITATION HYPOTHESIS

The view sponsored by Virchow and many others, that tumours resulted from the persistent stimulation of tissues by irritants, had much to commend it. It focused attention on extrinsic factors capable of affecting normal cells and so played an important part in advancing knowledge of occupational and experimental carcinogenesis. If in place of the term 'chronic irritation' we substitute 'carcinogenic stimuli' then the statements of this hypothesis by its earlier promulgators become modern. The hypothesis erred in emphasizing non-specific irritation instead of specifically carcinogenic stimulation, and in implying that tumours resulted from the over-stimulation of the cells by the irritants. The tissues were pictured as being "provoked" or "goaded" into anarchic growth. Study of pure chemical carcinogens has dispelled this misconception; these substances are not irritating in the ordinary sense. Nevertheless, as described in Chapter 4, non-specific injuries or irritations may act as co-carcinogens in augmenting or accelerating tumour formation in tissues already prepared by the action of carcinogenic agents.

Several elaborations of the irritation hypothesis require comment. The most important of these is connected with the part played by trauma in the genesis of tumours. There is scarcely any kind of tumour for which trauma has not been blamed in some or many cases; this applies not only to tumours of external and easily injured parts such as the integuments, breast, testis and bones but to those of deeply seated protected parts such as the brain, bronchi and other viscera. The possible part played by trauma in the causation of particular tumours will be discussed in the chapters of Part II; here it must suffice to make the general statement that simple injury of healthy tissues is rarely, if ever, a sufficient cause of neoplasia but, as already stated, injury can precipitate neoplasia in carcinogenically prepared tissues.

Another special extension of the irritation hypothesis is Handley's view 'that the origin of cancer is intimately associated with local obstruction of the lymph vessels' that lymph stasis lies at the root of cancer'. Admirable though much of Handley's work has been, most pathologists will agree that he has been unduly preoccupied with the lymphatic system both as regards metastasis and causation.

Several workers have postulated a relationship between tuberculosis and cancer. Of these the most insistent was Cherry who in a score of papers tried to show statistically that these two diseases were causally related "that a partnership exists between them", "that the two may be regarded as related forms of one disease" and 'that the mastery of the one should soon lead to the control of the other'. Cherry's arguments based mainly on mortality statistics, are nullified by the great degree of diagnostic error hidden in these (see Chapter 5). It is pertinent to add also that anyone experienced in necropsy work will know how frequently tuberculous lesions quiescent or active are to be found in adults.

- Morris L M (1927) *Amer Heart J* 3 219
- Nicholls A G (1927) *Canad Med Assoc J* 17 798
- Novak E (1927) *Amer J Obst Gyn* 14 470
- Offutt S R (1932) *Surg Gyn Obst* 54 490
- Ostertag B (1930) *Dtsch Z Nervenhe* 116 154
- PAGET, S (1889) 'The distribution of secondary growths in cancer of the breast *Lancet*, i 571 (One of the earliest and most pertinent commentaries on the anomalies of tumour dissemination)
- Piney A (1922) *J Path Bact* 25 140
- Piney A (1922) *Brit J Surg* 10 235
- Pitt G N (1887) *Trans Path Soc Lond* 38 398
- Pool E H and Dunlop G R (1934) *Amer J Cancer* 21 99
- Pusinelh and Geipel (1904) *Munch med Wschr* 51 2206
- Putschar W (1930) *Klin Wschr* 9 1699
- Putschar W (1930) *Z ges Neurol u Psych* 126 129
- von Recklinghausen F (1885) *Virchows Arch* 100 503
- Rice C O (1934) *Amer J Path* 10 407
- Robson G M (1928) *Arch Path* 5 751
- Rolleston H D (1893) *Trans Path Soc Lond* 44 109
- Rolleston H D (1912) *Diseases of the Liver Gall bladder and Bile Ducts* London
- Roth, W (1916) *Beitr path Anat* 61 42
- Russell D S and Cairns H (1930) *J Path Bact* 33 383
- SAMPSON J A (1931) Implantation peritoneal carcinomatosis of ovarian origin *Amer J Path* 7 423
- SAMPSON J A (1938) Implantation carcinoma of the tubal mucosa secondary to carcinoma of the ovary *Amer J Path* 14 395 (Sampson's papers are the best studies of peritoneal and tubal implantation and contain many beautiful microphotographs)
- Satke O and Salzer G (1932) *Virchows Arch* 284 632
- Scheidegger S (1935) *Z Krebsforsch* 42 93
- Schummelbusch C (1889) *Arch klin Chir* 39 860
- SCHMIDT, M B (1903) *Die Verbreitungswege der Karcinome* Jena (A classical study)
- Schmeel W (1909) *Frankfurt Z Path* 2 232
- Schwedenberg T (1905) *Virchows Arch* 181 295
- Ssobolew L W (1913) *Frankfurt Z Path* 13 344
- Stiles H J (1899) *Brit Med J* 1 1452
- Storjohann K R (1932) *Frankfurt Z Path* 43 80
- Stout A P and Murray M R (1942) *Arch Path* 34 951
- Taussig F J (1907) *Surg Gyn Obst* 5 511
- Teacher J H (1930) *J Path Bact* 33 491
- Thompson T and Evans W (1929) *Quart J Med* 23 135
- Toyosumi H (1903) *Virchows Arch* 191 70
- Trinea A J and Willis R A (1936) *Med J Austral* ii 222
- VIERTH, K (1895) Ueber rücklaenge Metastase in den Lymphbahnen *Beitr path Anat* 18 515 (A classical paper)
- Vogel L (1891) *Virchows Arch* 125 495
- Vorzimer J and Perla D (1932) *Amer J Path* 8 445
- de Vries W M (1934) *Beitr path Anat* 93 198
- van Wageningen W P (1930) *Arch Path* 20 199
- Wakasugi K (1910) *Beitr path Anat* 47 483
- Waldeyer W (1868) *Virchows Arch* 44 83
- Warren S (1931) *Amer J Path* 7 161
- Warren S and Meyer R W (1938) *Amer J Path* 14 605
- Weber O (1866) *Virchows Arch* 35 501
- Weller C V (1922) *J Cancer Res* 7 313
- Wells A H (1935) *Amer J Path* 11 1011
- Werner P (1913) *Arch Gynak* 101 725
- Werth (1884) *Arch Gynak* 24 100
- Willis R A (1930) *J Path Bact* 33 501

far as I know) has deduced from this relationship in time a relationship of cause and effect. But such a deduction would be no less logical than many that are drawn from time relationships—e.g. the relationship of the cancer death rate to a hundred and one aspects of modern 'life'.

(Hill *Principles of Medical Statistics*", 1939, p. 133)

The misconception that cancer is peculiarly a disease of civilization is now little more than a popular fallacy. Its latest expression was Cope's book, the title of which—*Cancer Civilization Degeneration*—sufficiently indicates its tenor. But this view has not been without some better-informed subscribers, notably Gilford, who cited Cope approvingly and who also saw in 'national degeneracy', in the bad habits and bad heredity of civilized life and in premature senescence of tissues, 'the basic causes of cancer'. Gilford's book is a useful compilation of references and facts about tumours, built, however, around this central preconception. (It is surely significant that Gilford was the describer of the condition of premature senility progeria.)

With regard to opinions such as the foregoing, the following facts discussed in earlier chapters may be recalled: that cancer is *not* peculiar to civilized peoples but occurs in all races of man and all classes of animals, that its incidence in different human communities depends on their respective age compositions, though its site incidence varies with local habits and exposure to special factors, and that increasing age brings more cancer, not because of senility of tissues, but because of the longer opportunity for the continued action of carcinogenic stimuli and for expiry of the long latent periods which intervene between the application of such stimuli and the appearance of the resulting tumours. That civilization causes cancer is, of course, true in the sense that many of the tumours of civilized man are evoked by identifiable carcinogens in his environment, such as tar, oils, arsenic or radium, and in the sense that carcinomas of the alimentary canal may well be due largely to avoidable dietetic habits or carcinomas of the breast to 'unnatural' reproductive and lactational habits. Effective prophylaxis by identification and avoidance of these carcinogenic factors is the main aim of experimental cancer research, and the great successes achieved in this field during the last three decades give the lie to Gilford's denunciation that 'nothing of any value has emerged from it'.

CANCER DIATHESIS

Probably the last serious attempt to uphold the old humoral hypothesis, that malignant tumours and their metastases were all manifestations of a constitutional cancerous dyscrasia, was at the meeting of the Pathological Society of London in 1874. It would be unnecessary to refer to the long obsolete notion of dyscrasia, did it not still appear occasionally in modern pseudo-scientific form. Thus, as recently as 1934, a well-known and experienced pathologist, Fischer Wasels, published a booklet contending that cancer can develop only in patients with a dietary alkalosis and recommending an elaborate dietetic and hygienic regimen for cancer sufferers. This included restriction of sugar, salt, cholesterol and vitamin B, administration of calcium, vitamin D, and splenic extracts, local

and will therefore realize the futility of attempting to correlate the incidence of cancer and previous tuberculous infection

PARASITIC HYPOTHESES

Parasitic hypotheses differ fundamentally from irritational hypotheses the latter pictured the irritation as bringing about irrevocable neoplastic cellular changes which then persisted independently of any further irritation the former suppose the responsible parasite to multiply in, and maintain the vicious growth of, the tumour Although tumours can be evoked by the presence of metazoal parasites, such as bilharzia or cysticercus these tumours are not relevant in the present connexion since they and their metastases do not depend for their continued growth on the presence of the parasites Bacteria, spirochaetes protozoa fungi and viruses have all in turn been blamed as the indwelling causes of tumour growth Only the last of these remain for serious discussion

Rous and his collaborators in America, Gye and Purdy in England and Blumenthal and co workers in Germany, have been the chief upholders of the view that mammalian tumours may like the filterable tumours of birds be due to a virus which multiplies in and maintains the pathological growth of the cells This question was discussed in Chapter 4 where it was pointed out that the filterable tumours of birds the Shope tumour of rabbits and Lucke's frog tumours are all decidedly peculiar diseases, and not necessarily valid exemplars of tumours in general At all events many attempts by experienced workers to demonstrate the presence of a filterable agent in malignant mammalian tumours have failed and the supposed successes of Blumenthal and others have been shown to be fallacious (see the experiments of Flaks and Wagner, cited in Chapter 6) The view, gaining increasing support, that the so called tumour 'viruses' may not be parasitic micro organisms at all but abnormal proteins of the cells themselves, is discussed below under 'Cytoplasmic hypotheses'

Webster depicted structures which he interpreted as virus inclusion bodies in cancer cells, he also believed that he could discern periodic fluctuations in the growth of tumours which he thought explicable only on the theory that they are essentially the outward representation of changes in the life-cycle of the causative agent However Webster's 'inclusion bodies' are well known to every histopathologist they are the same kinds of structures as the Russell's bodies and Plimmer's bodies, which long ago were thought to be cancer parasites of another kind—blastomycetes—but which we now know to be only abnormal cell products The cells of malignant tumours especially rapidly growing ones display a great variety of abnormal nuclear and cytoplasmic structures, some of which simulate closely the appearance of the inclusion bodies of virus diseases Virus workers must avoid being misled by these appearances With Webster's observations regarding periodicity in the recurrence and growth of tumours neither my own experience, nor that of other pathologists and clinicians with whom I have discussed the question is in accord and as far as I know no endorsements of them by other workers have been published

HYPOTHESES BLAMING CIVILIZATION

"It has been observed that while the death rate from cancer has been rising the sale of bananas in England and Wales has also been increasing No one (so

of the cells any intra-cellular parasite, any senescence or any genetic changes in the cells, but may consist in irreversible metabolic and cytoplasmic alterations occasioned by the application of carcinogenic agents, alterations which may well be conceived to differ in degree from tumour to tumour

Penfold (1922) likened tumour formation to the development of secondary papillae in bacterial colonies. These result from the selective action of poisons or particular nutritive substances favouring the growth of variants in the colony. Penfold suggested that a carcinogenic agent might play a similar part in selecting particular cell variants in the tissues.

Warburg (1925) attempted to explain tumour genesis as the result of oxygen deficiency in tissues causing selective survival of cells of high glycolytic powers—a hypothesis which subsequent work has shown to be untenable (see Chapter 8).

From his work on the effects of carcinogens on protozoa, Mottram (1942) was of the opinion that neoplastic change may well be cytoplasmic rather than nuclear. He rightly pointed out that the cytoplasm contains many important parts such as Golgi apparatus, mitochondria and chromidia, one of which might well be the important point of action of carcinogenic agents.

Haddow's work on the growth inhibitory action of carcinogenic substances led him to some important reflections on the genesis of tumours (1938 and 1944). Briefly his argument was as follows: carcinogenic agents inhibit the growth and metabolism of cells to which they are applied, the cells react to this by an alteration of their metabolism, which has "survival value and in effect confers a biological advantage", there thus appears "a new cell type with an increased rate of growth and, probably with other physiological properties which enable it to resist, or to escape from, the increasing restraint brought about by environmental changes". Haddow saw in this change a close parallel with the formation of vigorously growing secondary colonies in old bacterial cultures, as suggested earlier by Penfold. It is important to emphasize that the alteration does not consist in the acquisition of a new function so much as in variation in the property of growth which is normally possessed by the majority of cells.

With regard to the irreversibility of the change once established, Haddow (1944) drew attention to recent work on plasmagenes and cytoplasmic inheritance and to the view that cellular differentiation is determined by hypothetical particles in the cytoplasm. The production of different characters in cells with the same nuclear genes would thus be brought about by differential segregation of these cytoplasmic determiners at cell division. Now the degree of differentiation is an important individual character of tumours (see Chapter 8): tumours of a given cell type can be placed in a continuous series ranging from a near perfect reproduction of the histology of the parent tissue to a condition in which no specific differentiation can be recognized whatever. The extent of such departure is relatively stable for any given tumour. The chemical carcinogen produces a change in the habit of growth of the cell but as the change is quite permanent it persists indefinitely after the initial cause has disappeared. Hence the mechanism which permits unlimited growth must clearly reside in the cell itself. That it may reside partly at least in the cytoplasm is obviously a possibility for future investigation.

The possible nature of the agents of the filterable tumours is relevant here. Many of the plant viruses appear to be autocatalytic proteins of host cell origin.

the tumour we as yet know next to nothing The nature of this response is, however, no less understood than the nature of inflammatory response to a bacterial parasite When we say that the tubercle bacillus is the cause of tuberculosis', we state only part of the truth, and that the smaller part The tubercle bacillus does not cause tuberculosis in a test tube, or in some species of animals, or even in some human beings "Tuberculosis" involves two reagents, the bacillus and the susceptible tissue into which it is introduced The intrinsic properties of the tissues which render them susceptible and determine their tuberculous reaction are as yet unknown In this sense, then, the tuberculous reaction is no less mysterious than the neoplastic reaction, yet we do not attempt to explain the former by imagining a gene mutation or a "virus" in the altered cells When we can say of a particular tumour "That tumour resulted from the application of benzpyrene, or ultra violet rays or X-rays", then we know every bit as much about its cause as we know about the cause of tuberculosis or of any other inflammatory disease What makes the neoplastic reaction seem more mysterious to us than the inflammatory reaction is its irreversible character, and its long delayed onset perhaps long after the agent which evoked it has ceased to act At present we have achieved only vague glimpses of the possible nature of the cellular changes involved, but increasing knowledge of the mechanisms of cell growth and differentiation will undoubtedly clarify our view

REFERENCES

- Bashford E F Murray J A and Cramer W (1905) *Imp Cancer Res Fund Sci Rep* p 69
 Blumenthal F (1929) *Z Krebsforsch* 29 549
 Boveri T (1929) *The Origin of Malignant Tumours* Baltimore
 Boycott A E (1933) *Proc Roy Soc B* 113 291
 Cherry T (1943 and earlier) *Papers on Cancer and Tuberculosis* No 19 Melbourne
 Cohnheim J (1875) *Virchows Arch* 65 64
 Cope J (1932) *Cancer Civilization Degeneration* London
 Farmer J B Moore J E S and Walker C E (1903) *Proc Roy Soc B* 72 194
 Fischer Wasels B (1934) *Wege zur Verhütung der Entstehung und Ausbreitung der Krebskrankheit* Berlin
 Gilford H (1925) *Tumors and Cancers* London
 Gilford H (1934) *The Cancer Problem and Its Solution* London
 Gye W E (1925) *Lancet* ii 109
 Gye W E and Purdy W J (1931) *The Cause of Cancer* London
 Haddow A (1938) *Brit Emp Cancer Campaign Rep*
 HADDOW, A (1938) Cellular inhibition and the origin of cancer, *Acta Internat Union against Cancer* 3 342
 HADDOW A (1944) Transformation of cells and viruses *Nature* 154 194
 Haldane J B S (1934) *J Path Bact* 38 507
 Handley W S (1929) *Brit Med J* ii 607
 Handley W S (1931) *The Genesis of Cancer* London
 Lockhart Mummery J P (1934) *The Origin of Cancer* London
 McKillop L M (1929) *Med J Austral* ii 189
 Mettram J C (1942) *The Problem of Tumours* London
 NEEDHAM J (1942) *Biochemistry and Morphogenesis* Cambridge (The sections of this work on teratomas cancer and on differentiation should be read by every pathologist)
 NICHOLSON G W (1926) *The Nature of Tumour Formation* Cambridge
 NICHOLSON G W (1922-24 and 1933) *Studies on Tumour Formation* Nos II-VIII and XI-XIII *Guy's Hosp Rep* (The best critiques yet written on tumour hypotheses and the best presentation of proper views on causation)

a view expressed also by Stanley regarding the Shope papilloma virus (Chapter 6). Perhaps then, filterable tumour agents and plasmagens are related substances. At all events, the view that the former are parasitic micro organisms has steadily lost support. In 1925 Nicholson suggested that Rous sarcoma virus " might be not a virus, but ' a chemical substance produced by cellular action ' ". In 1933 Boycott said ' if one postulates a normal virus occurring in normal cells, one had better call it something other than a virus ' ". In 1942 Needham wrote, ' Why should we not call the primary evocator a virus, since it makes more of itself parallel with the histological change which it produces ? ' The objection to the virus theory of cancer lies in the fact that it emphasizes primarily the exogenous origin of uncontrolled specific proliferation. But on grounds of methodological simplicity ought we not to prefer the metabolism existing also in all the cells of the organism ?

Needham discusses in detail the chemical relationships of the carcinogenic hydrocarbons, the sex hormones and the group of sterols to which the embryonic evocating substances belong. He suggests that embryonic evocation, sex hormone action and carcinogenesis may well be related phenomena, and insists that one of the most important aspects of cancerous growth is its escape from the controlling pattern or individuation field of the tissues.

Modern biology is then, turning to the simplest theory of all regarding the nature of neoplastic change—the theory namely that the normal cells of the body are variable structures reacting in diverse ways to changes in their environment by changing their own habits of growth and metabolism, and that tumour cells are but variants of normal cells produced in response to external carcinogenic agents. Nicholson's prescient insistence on this principle is summarized in the following citations from his Study No. XIII (1933): ' I see in tumour formation the shifting *more or less* of the somatic ratio in the direction of accelerated growth with consequent—necessarily—retarding of physiological action (and its morphological expression—histological differentiation). The secret of tumour formation lies for me in the mechanism that determines the new ratio. To

explain tumour formation with a misconception like autonomy or uncontrolled growth or with a hypothesis like a virus, chromosomal malformation or mutation *et hoc genus omne* is idly to scratch the surface. For the problem is rooted in the very being and coming to be of organismic evolution and individuation, development and existence, form and function. Our knowledge of tumour formation is a pretty accurate measure of our understanding of growth and development. Advance in either means advance in both. We have begun to ask crucial questions of biology, and are beginning to get answers. We are beginning to do without unphysiological, unbiological and essentially unnatural and incomprehensible morbid reactions of the organism and to see that everything is physiological except the purely adventitious extrinsic stimulus. We are beginning to see that tumour formation is reaction to excitation, growth and differentiation of cells capable of these functions, consequent acquisition of characters, maintenance and transmission to future cell generations of the characters thus acquired—in sum the first principles of individuation and life.

Briefly, tumour formation is the final product of the cumulative response of cells to certain environmental stimuli. Of recent years we have learnt a great deal about some of these stimuli of the all important cellular response which yields

CHAPTER 12

RECAPITULATION

DEFINITION

OUR DEFINITION of a tumour, as *an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change*, can now in the light of Chapters 4, 8 and 11, be much better appreciated. Nicholson's "failure of co-ordination", or Needham's "escape from the controlling pattern or individuation field", is the essential quality in a neoplasm. This escape is bound up with an irreversible change in the metabolism and multiplication of the cells—a change which is transmitted indefinitely to their descendants and which persists independently of the carcinogenic stimuli which initiated it. This permanent and transmissible habit of excessive uncoordinated growth distinguishes tumours from all other pathological overgrowths, whether hyperplasias, reparative proliferations or malformations.

CLASSIFICATION AND NOMENCLATURE

The only fundamental basis of tumour classification is histogenesis, i.e. according to the type cells from which tumours spring and of which they consist. All other features, such as rate of growth, degree of differentiation, and, with these, degree of innocence or malignancy are subsidiary. The parenchyma of most tumours consists of cells of a single type, so that their histogenetic classification and nomenclature run parallel with the histological grouping of normal tissues. Some tumours, however, are composite, containing two or more neoplastic tissues; many of these, namely, the mixed tumours of infancy and the teratomas, arise during early development from still immature tissues. Apart from the important distinction between the relatively rare truly embryonic tumours, which arise from and continue to consist of embryonic tissues on the one hand, and the common tumours of adult tissues on the other hand, the embryonic origin of tissues are of no interest in tumour classification. Tumours are anomalies of growth and differentiation of particular kinds of tissues, the original germ layer derivations of these are irrelevant. Causation also is irrelevant in classification: different carcinogens applied to a given tissue evoke similar tumours while a single carcinogen applied to different tissues may evoke a variety of tumours.

INNOCENCE AND MALIGNANCY

'Innocent' and 'malignant' are relative terms, of value in the art of prognosis but not denoting distinct species of tumours. The individual tumours of a particular cell type usually show a complete range of structure and behaviour, from those which grow slowly, attain high differentiation and remain non-invasive and local to those which grow rapidly, differentiate poorly, invade and

REFERENCES

- Penfold W J (1922) *Med J Austral* i 460
- Ribbert H (1907) *Beitrage z Entstehung d Geschwulste* Bonn
- Rous P (1935) *Harvey Lectures* p 74
- ROUS P (1936) The virus tumors and the tumor problem *Amer J Cancer* 28 233 (An authoritative exposition of the virus hypothesis of tumours)
- Russell E S (1930) *The Interpretation of Development and Heredity* Oxford
- Warburg O (1925) *J Cancer Res* 9 148
- Webster J D (1940) *The Periodicity and Cause of Cancer* London

and fallacies of statistics in general, but also with the medical aspects of his problem, including the bases and reliability of diagnosis, the use of pathological nomenclature, the efficacy of treatments, the methods of recording, etc. Unless he has this dual knowledge, he is unlikely to escape falling into some unsuspected trap, and, if he has it he will realize how limited the applicability of the statistical approach to many of the problems connected with tumours.

Purely statistical errors are often committed by writers of papers on tumours. But more important even than these, are the frequent errors of tumour diagnosis—errors which of course if present in any considerable proportions, necessarily vitiate any statistical analyses whatever. The main theme of Chapter 5 was to show what proportions of the clinical diagnoses of the particular kinds of tumours are likely to be erroneous, and it was concluded that, except for the more accessible tumours, such as those of the skin, breast, buccal cavity or uterus, general clinical diagnosis is fraught with such a high degree of error that many statistical studies are valueless. Surgical or post-mortem series of cases of proven pathological nature afford valid data for statistical deductions within limits imposed by the selected nature of the material. But for many major statistical problems such selected series are of course unsuitable. For these and other reasons, comparisons of the mortality figures of different countries or of clinical records in different communities or clinics, and estimates of trends in tumour incidence, must be viewed with great caution.

TUMOURS IN ANIMALS

Tumours resembling those of man occur in all classes of vertebrates, in both the wild and captive state, and there is no main kind of human tumour of which counterparts do not occur in one or more other species of mammal. The study of animal tumours is often helpful in elucidating the histogenesis of the corresponding human ones, and the incidence of particular tumours in mammals may well give clues regarding the responsible carcinogenic factors. Transplanted tumours are of limited value in the study of many of the problems of tumour behaviour or response to therapeutic agents, for these purposes, spontaneous tumours or those evoked experimentally by carcinogens are often preferable.

THE MODE OF ORIGIN OF TUMOURS

Contrary to the still prevalent unicentric idea of tumour origin—a relic of the erroneous hypotheses of Cohnheim and Ribbert—tumours do not arise from single minute foci but from considerable fields of prepared tissue. Many small, and some large, tumours still show clear evidence that tumour genesis, the transformation of the tissue of the susceptible field into tumour, was still in progress when the tumours were excised. Should excision have failed to remove the whole of the tumour formative field, recurrence of the growth may ensue, not from tumour residues as such, but from new areas of cancerous change in the residual tissue of the field. In extensive potentially cancerous fields, multifocal development of cancer is often to be observed, good examples include the multiple carcinomas in polyposis of the colon or in xeroderma pigmentosum or in the

disseminate There is a broad parallelism, but with many individual exceptions between degree of malignancy and degree of anaplasia, a parallelism long recognized by pathologists as of value in prognosis Attempts to prognose by 'grading' tumours numerically however, though they may impress the clinician by their spurious appearance of precision are always highly arbitrary and often fallacious A high degree of structural organization is compatible with malignancy, and poor organization with innocence 'Malignant cachexia' does not exist, the debility, malnutrition and anaemia of many cases of advanced malignant disease are merely the results of interference with important bodily functions by the tumours

THE EXPERIMENTAL PRODUCTION OF TUMOURS

Recent achievements in this field of research have been epochal Tumours of almost all kinds have been produced by pure chemical substances or by various physical agents and many of these experimentally identified carcinogens are clearly the same as those responsible for occupational and other tumours in human beings Already the experimental work has thus shown the way to effective prophylaxis of certain human tumours e.g. mule spinner's cancer, actinic skin cancers, radium and X-ray cancers, aniline worker's cancer of the bladder etc As the experimentalist goes on as he will do to identify more and more carcinogens in our environment—in our food and drinks, our occupational materials and reagents, our tobacco smoke, drugs and cosmetics—so an extending basis for prophylaxis will be laid Whether and to what extent the people generally will be prepared to avoid the noxious factors detected will be the concern not of the experimentalist but of politicians, teachers, social workers and public health authorities

Not only has experimental work disclosed a great variety of exogenous carcinogens but it has shown also that endogenous carcinogens may be formed in the body itself as the result of disturbed hormonal states or other pathological conditions For obvious reasons, work in this field is more difficult and complex than the search for exogenous carcinogens but future research will identify the chemical carcinogens formed in diseased tissues and will unravel the factors involved in their production This knowledge will probably elucidate the causation of most of the tumours of the breast, uterus, prostate and ductless glands and will point the way to their prevention

In yet a third way experimental carcinogenesis is full of great promise By studying the chemical properties of carcinogens, their structural and functional effects on tissues, their absorption, metabolism and fate in the body and the phenomena of anti-carcinogenesis and co-carcinogenesis it is not unlikely that something may be learnt of the nature of the neoplastic change in cells, the ultimate secret of tumour formation

THE STATISTICAL STUDY OF TUMOURS

Many pitfalls beset the student of tumour statistics Before venturing on any deductions whatever—even as regards such seemingly simple questions as the age incidence of a particular kind of tumour or the relative frequencies of tumours of different kinds—he must be thoroughly acquainted, not only with the methods

important general property of tumours, their growth is susceptible to external influences. Mitotic activity varies in different parts of a tumour or in metastases in different situations. Some innocent, and occasional malignant, tumours spontaneously cease growing and retrogress, some malignant tumours show unaccountable temporary arrests of growth, long delayed recurrence or long delayed metastasis, the growth of some tumours, especially those of hormonally controlled tissues, varies with the endocrine state of the patient or with the administration of particular hormones, carcinogenic substances inhibit tumour growth. All these facts encourage the hope that, when research has elucidated the controlling factors, an effective chemotherapy of cancer may not be impossible of achievement.

THE DIRECT SPREAD OF TUMOURS

As a tumour increases in bulk by proliferation of its cells, it finds accommodation in the tissues in one or both of two ways—by *expansion* or by *infiltration*. Invasiveness does not depend on any single property of the tumour cells, nor on any special changes in the invaded tissues, it is one attribute of the neoplastic cellular change as a whole, differing from tumour to tumour but nearly constant in each.

Invasiveness confers on a tumour the power to penetrate into any or all available interstices or preformed channels in the tissues and to spread in these away from the primary site for short or long distances. The paths of invasion are intercellular and intracellular spaces, lymph vessels, blood vessels, coelomic and cerebrospinal spaces and epithelial cavities. Invasion of preformed paths sets the stage for metastasis by transport.

METASTASIS

Metastasis means the transfer of detached tumour particles within vascular, coelomic, cerebrospinal or epithelial channels, and their successful lodgement and survival to produce discrete secondary growths at new sites. It is a form of natural grafting or transplantation of the tumour from site to site. Not all grafts are successful; dissemination and lodgement of tumour particles may occur but no metastases develop, the arrested cells failing to multiply or survive in their new environment. Abortive tumor embolism is commonly demonstrable in the lungs but doubtless occurs in most other tissues also, it accounts for many of the peculiarities of distribution of metastatic growths. Elucidation of the chemical and other factors which determine the success or failure of disseminated tumour cells to survive and grow in new sites might assist in the search for effective chemotherapeutic agents. The great series of grafting experiments already performed for us in the dissemination and metastasis of tumours is thus worthy of close study, this should be supplemented by experimental investigations of metastasis like those described in Chapter 6.

The study of metastasis is of immediate practical importance to the clinician not merely because of its obvious bearing on operability and prognosis, but also because metastatic growths may be the first or main manifestations of otherwise symptomless or unsuspected primary tumours. As was noted in Chapter 5 many misdiagnoses are due to secondary growths masquerading clinically as

exposed skin of the fair skinned farmer or sailor or in the cystic hyperplastic breast

The field origin of tumours is not only clear from structural studies but from experimental work. When a carcinogen is applied to a tissue it is not applied to a single minute focus but to a more or less extensive field of the tissue. Visible tumour formation usually commences at one or more small foci in that field but the neoplastic change extends from these to other parts of the field. The distribution and timing of this change is determined, no doubt by the distribution and intensity of the carcinogenic stimulation to which the whole field has been subjected and to co carcinogenic injuries to which it may also have been exposed. The spread of tumour genesis in the field does *not* imply the spread of any parasite or chemical influence from tumour cells to adjacent normal ones.

THE STRUCTURE AND GROWTH OF TUMOURS

Most tumours show remarkable structural individuality and stability. Throughout a long metastatic career or during a long series of transplantations a particular tumour usually maintains not only its own characteristic degree of organization and general rate of growth, but also many minor peculiarities of structure such as its range of variation, metaplastic propensities, cytological details and the nature and amount of stromal reactions excited by it. Clearly then, whatever the fundamental nature of the neoplastic change may be it varies in degree, and perhaps in minor ways in kind also from tumour to tumour.

The range of structural variation in a single tumour is often such as to preclude its allocation to any particular histological sub group within its class. Such histological names as 'spheroidal cell carcinoma', 'adenocarcinoma', 'oat-cell carcinoma', etc. have only a descriptive value to designate the predominant structural variants in particular tumours. They do not denote distinct species, the species are *carcinoma of the breast*, *carcinoma of the bronchus*, etc., and histological sub division of these is always arbitrary and often quite inapplicable. A single tumour may show all the varieties of structure of which its species is capable.

Anaplastic tumours, especially carcinomas, often display misleading microscopical appearances simulating those of other kinds of tumours. Diffusely growing carcinomas have often been misdiagnosed as sarcomas. The diagnosis 'carcino sarcoma' has been particularly fallible. The great majority of tumours so designated have been pleomorphic carcinomas, truly composite carcino sarcomas do occur but are very rare. The mammary fibro adenomas however, are truly composite growths the fibromatous component of which sometimes becomes sarcomatous.

Naturally enough the cells of rapidly growing tumours often show abnormalities of structure and metabolism but in neither their cytology nor chemistry have the cells of well differentiated tumours been shown to differ from normal cells in any significant or constant characters. That tumour cells are permanently altered cells there is no doubt, but the alteration is more subtle than our microscopical and chemical methods have so far proved capable of detecting.

While relative constancy of individual structure and habits of growth is an

CHAPTER 13

EPITHELIAL TUMOURS OF THE BREAST

HISTORICAL INTRODUCTION

FOR MANY reasons—notably its great frequency and lethal properties, its nearly complete restriction to the female breast, its now proven relationship to the hormonal control of the breast and to disturbed breast function, and its experimental production—mammary carcinoma has excited more interest than any other kind of tumour

Because of the external situation of the breast, carcinomas and other tumours of this organ were no doubt amongst the first tumours to be recognized and named by the ancient Greeks. Hippocrates and his contemporaries knew of cancer of the breast, but, earlier still and perhaps the first specifically reported instance of breast tumour, was that recorded by Herodotus. Atossa, the daughter of Cyrus and the wife of Darius I about 520 B.C. 'had a tumour on her breast, after some time it burst, and spread considerably. As long as it was small she concealed it, and from delicacy informed no one of it, when it became dangerous, she sent for Democedes and showed it to him.' Democedes is said to have cured it, but by what means or how permanently we are not told, and of course, as with all early records, we cannot be sure of the nature of the lesion. Early in the first century A.D., Celsus practised amputation of the breast for early cancers, but considered that operation on advanced cases only aggravated the disease (Castiglioni). Indicative of the persistence of the doctrine of humours is the following statement from Paul of Aegina in the 7th century. "Cancer is particularly frequent in the breasts of women, because owing to their laxity they readily admit the thick humours which occasion it. For cancers are formed by black bile over-heated, and if particularly acrid, it is attended with ulceration.

The veins are filled and stretched around like the feet of the animal called cancer (crab) and hence the disease has got its appellation. But some say that it is so called because it adheres to any part which it seizes upon in an obstinate manner like the crab." Severino's account of 'strumas of the breast' (1632) is noteworthy because for the first time it distinguished between benign and malignant tumours of the organ and also contained passages suggesting that the author recognized what we now call cystic hyperplasia as a pre cancerous condition.

The state of knowledge of tumours of the breast—and of tumours generally—in the latter part of the eighteenth century is well shown by the following citations from John Hunter's lectures. Speaking of "the scrofulous breast (meaning the fibro adenomatous), Hunter described a tumour "which came on at the age of twenty-six, and increased gradually to thirty eight. It was sixteen or eighteen pounds in weight. In this case there was no disease leading to the axilla as in cancer, so that I dissected it out and it healed kindly. It was perfectly circumscribed which is never the case with cancer, when of any size. Cancer may be

primary ones. Clinicians still have far too little knowledge of this important source of diagnostic mistakes.

HYPOTHESES OF NEOPLASIA

As in so many other difficult fields of research, fantasy has often been substituted for the difficult admission "Ignoramus." But while the imaginative have been producing a crop of conflicting theories, histopathologists and experimentalists have been building up a secure foundation of knowledge of tumour causation and behaviour and—healthiest omen—pathologists are beginning to pay attention to biologists, and biologists to pathologists. All are coming slowly to realize that progress in embryology, in genetics, in cytology, in biochemistry, in endocrinology and in pathology are all inextricably linked, that pathology is extended physiology and that disturbances of growth studied by one specialist are of interest to all. Tumours constitute one of the major forms of growth disturbance in response to certain external agents—carcinogenic agents—applied to cells. Many of these external agents are being identified, the nature of the internal response, the neoplastic change in the affected cells still needs elucidation. But, that this will come with increasing knowledge of cell chemistry, of the mechanisms of cell differentiation and co-ordination and of the mode of action of carcinogens, there is no doubt. The first steps in this elucidation have been taken when it has been completed it will be found that neither embryonic cells nor their reverse—senescent cells, neither ultra-microscopic parasites nor disordered chromosomes nor mutant genes are concerned in the change from normal to neoplastic cells.

contamination" Of incurable cases, "When the glands become indurated the fluids are not absorbed, in consequence of which there is a stagnation and extravasation of serum causing oedema of the parts around. The arm and the integuments of the chest below, swell, and the fingers are sometimes rendered immovable, and very painful. In this stage sympathetic cancerous tumours often arise at a distance, and hectic fever comes on." Hunter rejected the view that cancer produced a specific kind of cachexia "this is no more than the effect of all long continued irritations, or sores which are not disposed to heal, but no peculiar effect is produced from this affection on the constitution. Cancer appears to give rise to no constitutional symptoms, except such as would arise in other diseases from the long continued wearing pain and perpetual discharge."

In its main essentials then Hunter's knowledge of mammary cancer was surprisingly complete—about as complete indeed as it could be, prior to the advent of histopathological methods and the more precise means these afforded for the specific identification of tumours. Cheatle and Cutler's admirable monograph is the culmination of the histological study of mammary tumours.

TYPES OF MAMMARY TUMOURS

Epithelial tumours of the breast comprise

- (1) Fibro adenoma and adenoma
- (2) Duct papilloma and papillary cystadenoma
- (3) Carcinoma
- (4) Paget's disease of the nipple

While the first of these is a distinct sub group, the other three are closely related to one another. No sharp distinction can be drawn between benign papillomas and papillary carcinomas of the ducts, papillomas may coexist with invasive carcinoma, carcinoma of the mammary epithelium almost always coexists with Paget's disease, and all three forms of growth may occur in the one breast.

The relative frequency with which the four types of tumour are encountered in surgical practice is indicated roughly by the following figures, showing the numbers of the microscopical identifications of all surgically removed mammary tumours made at the Alfred Hospital, Melbourne over a period of 14 years.

Carcinomas of female breast	—	—	—	—	—	550	cases
Carcinomas of male breast	—	—	—	—	—	2	,
Fibro adenomas	—	—	—	—	—	130	,
Benign papillomas	—	—	—	—	—	15	„
Paget's disease	—	—	—	—	—	6	,
Sarcoma	—	—	—	—	—	1	case

The number of papillomas is probably underestimated, it includes only simple localized growths unaccompanied by carcinoma, and excludes some papillomas present in cancerous breasts. Paget's disease was accompanied by intra-mammary carcinoma in all 6 cases. According to these figures the surgeon might expect to see mammary carcinoma about 4 times as frequently as

so at first, when small and loose in the cellular membrane, but when as large as a large egg it affects the surrounding parts and is more diffused. True scrofula, however if attended with inflammation will also adhere and diffuse and lose itself in the surrounding parts, so as to put on a cancerous appearance'. He described how, in well established cancer, the skin will be less movable, the nipple more or less retracted and the lymphatic glands going to the axilla will swell. In cancer the surrounding parts that are affected by continued sympathy also become cancerous near the skin that is all the parts become blended in one mass. When scirrhus is entirely let alone it is commonly very slow. A small lump in the breast may sometimes continue for many years, but whenever inflammation takes place its progress is accelerated. Sometimes the first symptom of a cancer in the breast is a bleeding from the nipple.

That Hunter recognized the surgical importance of the multicentric origin of some mammary cancers and their association with cystic changes in the breast is shown by the following passage. It (cancer) often arises in distinct points of the same breast but seldom at the same period and some of these may be so much in their infancy when the operation is performed as not to be observable, but afterwards increase and require a second operation. The surrounding substance of the breast has often little tumours, sometimes containing a blackish fluid these may be called cancerous hydatids. It is therefore best to extirpate the breast completely at once to remove the whole complaint.

Hunter's views on operability also were remarkably sound. Now to know if a cancer is proper for operation two things should be considered viz the cancer itself and its consequences. Great attention should be paid to the tumour, whether it is movable or not for as the disease is further extended so the parts are more united to the tumour. If the tumour is not only movable but the part naturally so then there is no impropriety in removing it with regard to the tumour itself but before removing it we must consider if there are any consequences. We should examine for example the glands in the groin or axilla to ascertain if they are thickened or swollen. All the above circumstances being considered and no objections existing the breast may be safely removed and if any consequent cancers easy of extirpation are found they may be safely removed also. But it requires very great caution to know if any of these consequent tumours are within proper reach for we are apt to be deceived in regard to the lymphatic glands which often appear movable when on extirpation a chain of them is found to run far beyond out of our reach which renders the operation unsuccessful. As this is not easily known I would in most cases, where the lymphatic glands are considerably enlarged, advise that the case should be let alone'. Surely advice as sound to day as then!

Regarding post operative recurrence Hunter observed. This is either in the cicatrix or in the lymphatic glands. I have sometimes seen after the operation the glands under the clavicle swell and push out the clavicle. The contamination extends in other instances on the inside of the sternum in the course of the internal mammary artery. Sometimes these consequent cancers appear long after the operation even years. In an earlier lecture he had stated 'I have seen instances where it was years after all continuance of the cause was removed before the glands in the armpit had taken on diseased action after

(a) Age and sex incidence

Fibro adenomas are rare before puberty, but are the commonest mammary tumours between then and the twenty-fifth or thirtieth year. Most of them are discovered during this period, but some, especially those with predominant intra-canalicular structure, do not appear until later. The large intra canalicular tumours are seen usually in middle aged or elderly people, though there has often been a long history of an enlarging lump.

Fibro adenomas are very rare in the male breast, Chentle and Cutler cite recorded cases, Scarff and Smith record 4 examples in a series of 65 mammary lesions in males.

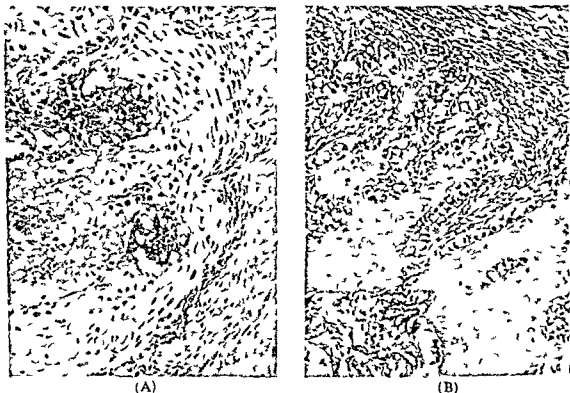


FIG 53 —Fibro adenoma of dog. A = calcifying cartilage. B = bone ($\times 120$)

(b) Fibro adenomas in animals

These growths have rarely been observed in any species of mammals other than dogs and rats in both of which however they occur frequently.

(i) *Dogs*—Mammary fibro adenomas are common in bitches of most breeds (Feldman, Schlotthauer, and see the table in Chapter 6). They are usually found in middle aged or old animals but are often known to have been present for some years or are large tumours clearly of long duration when first noticed. They are often multiple in one breast or in several breasts, are often associated with cystic hyperplastic changes and sometimes carcinomatous changes supervene in them. In the 17 dogs with fibro adenomas studied by Rudduck and me the animals ranged in age from 6 to 12 years, the tumours ranged from 1 to 11 centimetres in diameter, were multiple in 5 cases, and showed supervening carcinoma in 2 cases. The microscopical appearances of cartilage may be simulated

fibro adenoma and about 40 times as frequently as simple papilloma while Paget's disease may accompany mammary carcinoma in about 1 per cent of cases

FIBRO-ADENOMA AND ADENOMA

I apply these names in the usually accepted sense distinguishing fibro adenoma sharply from duct papilloma. Because of the papillary pattern of the intra-canalicular type of fibro adenoma some writers (e.g. Saphir and Parker) have



FIG 51 —Fibro adenoma of dog showing intra-canalicular structure. The tumour measured 11 centimetres in diameter ($\times 80$)



FIG 52 —Fibro adenoma of dog showing glandular tissue and cartilage in close juxtaposition ($\times 129$)

called this growth fibro papilloma but I think it better not to confuse the fibro adenomas and duct papillomas even in name for the two have little in common

(c) *Mode of origin*

By examination of the breast tissue around fibro adenomas, Nicholson's and Cheatele and Cutler's observations on their mode of origin is readily confirmed. The surrounding tissue almost always shows some degree of lobular hyperplasia of adolescent type ("mazoplasia" of Cheatele, "adenosis" of Dawson) with the development of multiple small satellite fibro adenomas or incipient fibro adenomatous foci. These enlarge and coalesce with the main mass to form a lobulated



FIG 55 —Intra-canalicular fibro adenoma ($\times 50$)

tumour, the early growth of which is therefore by accretion as well as by proliferation. Transitions from breast to tumour tissue are often to be seen and the tumours, though seeming to be well circumscribed and easily shelled out are not strictly encapsulated. The bed of tissue around a fibro adenoma is thus a field of potential similar change, and following simple enucleation of the growth recurrence may ensue from new foci of growth developing in this tissue. The proper surgical treatment is therefore excision of the segment of breast containing the tumour. Multiple fibro adenomas are not uncommon, they are usually in close proximity to one another, but are sometimes remote or bilateral.

(d) *Structure*

Two kinds of pattern are recognized in fibro adenomas (i) peri canalicular or peri acinar, and (ii) intra canalicular, the former predominating in the tumours of youth the latter in those which appear after the age of 30. There are not two distinct types of tumour, however many fibro adenomas show both kinds of structure.

(i) *Peri canalicular structure* —This shows sim normal appearance set in a variable, usually exces peri ductal connective tissue as in Fig 54. This plump fusiform fibroblasts and wavy delicate non co

ry ducts of ne of characte ured tissue he proport

by epithelial cells scattered in mucinous secretion as in the pleomorphic tumours of salivary glands, but true cartilage or bone often develops by metaplasia in the fibromatous tissue of the tumours. Cartilage or bone was present in 6 of our 17 cases, and in one case haemopoietic marrow had developed in a mass of bone. Apart from the frequent presence of these metaplastic tissues, the canine tumours are in most respects similar in structure to the human ones (See Figs 51-53)

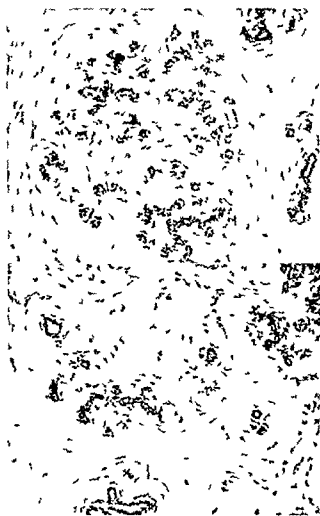


FIG. 54—Fibro adenoma of rat ($\times 120$)

(ii) *Rats*—Fibro adenomas are the most frequent mammary tumours in rats (Curtis *et al*, Ratchiff, Wright *et al* and see Fig 54). Different tumours contain the glandular and fibromatous components in all possible relative proportions from nearly pure adenoma to pure fibroma. The tumours are transplantable and by successive transplantation the epithelial component suffers elimination from some tumours leaving pure fibroma and in some instances this becomes sarcomatous (Robinson and Grauer, Emge and see Chapter 6).

persistence of adipose tissue cells in the tumours (Fig 64) and the metaplastic development of cartilage or bone in the fibromatous component. This last feature which is common in the canine tumours is rare in the human ones, Cheate and Cutler saw it in only two cases, and I have seen it only once

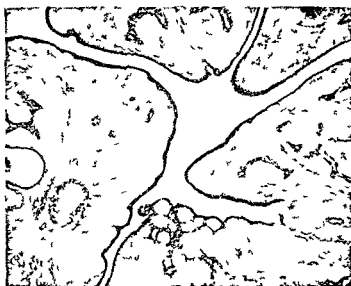


FIG 57—Intra canalicular fibro adenoma with hyalinization of connective tissue from a woman of 28 ($\times 50$)

Occasionally, mucinous change in the fibromatous tissue is prominent enough to give it a slimy feel, a bluish colour in haematoxylin stained sections and meta chromatic staining properties with polychrome dyes, the name "myxofibro adenoma" is then appropriate. Nicholson, Dawson, Geschickter and Lewis, and others have shown that fibro adenomas participate in the mammary changes of pregnancy and lactation. Calcified spherules occur in the epithelial spaces of some of the old dense fibro adenomas.

(e) *Giant fibro-adenoma*

Valuable reviews of the large soft or cystic fibro adenomas sometimes seen in the middle aged or elderly have been published by Lee and Pack (1931) and Owens and Adams (1941) who also cite Johannes Muller's classical and excellent account of these growths (1838) under the title "cystosarcoma phyllodes". These tumours develop from small pre-existing fibro adenomas of the usual type. They often enlarge slowly for several years and then may suddenly start to grow more rapidly. They have often attained a huge size, the average weight in the cases reviewed by Lee and Pack was $7\frac{1}{2}$ lbs, and Mackenzie saw a tumour of 35 lbs. They are well circumscribed, lobulated and often cystic, and they distend the skin and may suffer accidental ulceration, infection and fungation. But in the great majority of cases they are non-invasive, non-metastasizing tumours, with good prognosis following surgical removal.

Microscopically the bulky masses of polypoid and cystic growth show luxuriant fibro adenomatous structure, usually of the intra canalicular type, and the fibro matous component often shows prominent myxomatous changes and cellular areas of sarcomatous appearance. Infrequently, the epithelium lining the clefts

of epithelial and connective tissue vary greatly. Adenomas, with ducts and acini forming the bulk of the tumours, seen usually in young people, are rare. Cheatele and Cutler give 4 examples. Usually the fibromatous tissue exceeds the epithelial in bulk. the latter may be very scanty and the tumour little short of pure fibroma. Proof of the purely fibromatous character of a breast tumour therefore requires very thorough search of many parts for the possible presence of epithelial elements. I myself have not yet encountered a pure fibroma.

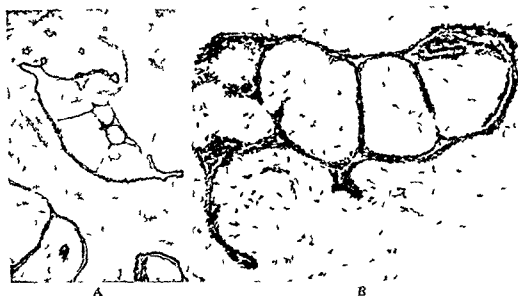


FIG 56 —Intra-canalicular fibro adenoma compression atrophy of epithelium (A $\times 40$ B $\times 96$)

Fibro adenomas which appear during puberty or adolescence often show a structure closely similar to that of the normal breast tissue of the same age and "frequently no histological evidence of a capsule is present even when, to the naked eye the defined tumour area suggests an easy shelling out (Dawson). Perhaps then no sharp distinction is possible between the rare diffuse mammary hyperplasias of adolescence and the commoner localized fibro-adenomas of the same period.

(ii) *Intra canalicular structure* —This arises by proliferation of the sub epithelial tissues in a coarsely papillary pattern with invagination distortion and distension of the ducts. Plane sections show to the naked eye a laminated appearance like sections of a crinkled cabbage and micro sections reveal the complex dove tailed shapes and interlocking of the branching convoluted parts (Figs 55 and 56). The epithelium clothing the fibromatous projections often suffers atrophy by stretching or compression and it sometimes disappears in places, leaving a raphe like junction of adjacent connective tissue papillae (Fig 56). During their early growth the tumours show the same delicate loose-textured fibromatous tissues as in the peri canalicular type but old tumours often show condensation and hyaline change of the connective tissue (Figs 57 and 58).

Unusual structural features of fibro adenomas include the presence of smooth muscle fibres in the connective tissue (Cheatele and Cutler) the inclusion and

(f) Malignant change in fibro adenomas

While most huge fibro-adenomas—even those of rapid growth and with suspiciously cellular areas—are benign in that they fail to invade neighbouring tissues or to metastasize, occasional tumours of this kind prove to be malignant. Almost always, the malignant change involves the connective tissue component, which shows anaplastic cellular growth with plentiful mitotic figures, from which recurrence or metastasis ensues. White (1940), however, described a case in which extensive recurrence and metastasis followed removal of a large rapidly growing tumour of 2 years' duration in a woman of 34, and his Fig. 7 suggests that the pulmonary metastases may have contained epithelial components as well as sarcomatous growth, but no descriptive details are given.

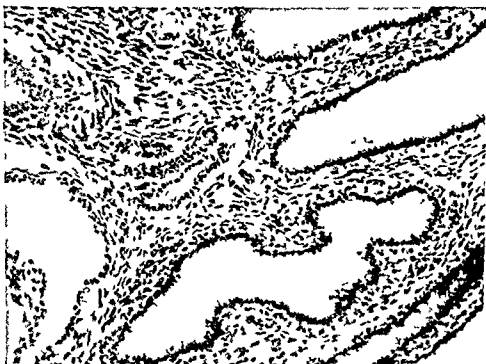


FIG. 59—Case II Giant fibro adenoma ($\times 120$)

Carcinomatous change in a fibro adenoma, if indeed it ever occurs, must be extremely rare. It was not observed in the extensive experience of breast tumours of either Cheatle and Cutler or Dawson. Carcinoma and fibro adenoma may coexist in one breast, as in Cases VIII and IX below, and carcinoma may invade a fibro adenoma. Tudhope described an unusual tumour which contained different areas of fibro adenomatous, carcinomatous and apparently sarcomatous structure together with the formation of cartilage and osteoid tissue by metaplasia of the stroma. He believed, possibly correctly, that the carcinoma had arisen from the epithelium of the fibro adenoma, so that this case may exemplify the extremely rare event of conversion of a fibro adenoma into a composite carcinoma sarcoma by simultaneous malignant change of both components. Budd and Breslin also studied an unusual composite tumour of the breast region, this had been present for 28 years and had grown actively only recently, microscopically it consisted of mingled active carcinoma and osteogenic sarcoma. Mallory's

and cysts shows squamous metaplasia in parts. The following 3 cases illustrate many of the characters of these tumours.

Case I—A married woman aged 77 had had a slowly enlarging tumour of the left breast for 40 years. It had recently become inflamed and ulcerated. Examination showed replacement of the breast by an irregularly hemispherical lobulated tensely cystic tumour.



FIG. 58—Fibro adenoma from an elderly woman showing hyalinization of connective tissue and atrophy of epithelium ($\times 120$)

25 centimetres in diameter with an infected fungating area on its lower surface. Simple mastectomy was performed with a good result. The tumour weighed 9 lbs. and it had the structure of a simple fibro adenoma mainly of peri-canalicular type with abundant not very cellular connective tissue. The patient died of pneumonia 4 months later. Necropsy showed no residual or metastatic growth but a large papilliferous multilocular ovarian cystadenoma was present.

Case II (Dr Ian Pender's case)—The patient was a multipara aged 45 who had breast fed her children and had had no previous breast trouble and whose menstrual history was normal except that the menses had not commenced until the 18th year. Following a moderately severe blow on the left breast in March 1937 enlargement of the breast was noticed in May. This increased rapidly and radical amputation was carried out in October i.e. 5 months after the tumour was first noticed. The patient remained well several years later. *Naked eye examination* showed a well-defined rounded tumour 3.3 centimetres in main diameter and 1350 grammes in weight. The cut surface of which had the appearance of a soft oedematous fibro adenoma. The remainder of the breast tissue and the axillary contents appeared normal. *Histology* (Figs 59-61)—The structure is that of a fibro adenoma mainly intra-canalicular but partly peri-canalicular in pattern. The epithelium lining the irregular glandular spaces consists of plump cubical or columnar cells which show a moderate number of mitoses. The connective tissue is very cellular in most places consisting of large fusiform cells many of which show mitotic figures. Collagen fibres are plentiful in some areas but almost absent in others.

Case III (Mr Balcombe Quick's case)—A married woman under 40 years of age had noticed a small lump in the breast for 2 years. This had grown rapidly in the last 6 months. The breast was amputated. The tumour was well-defined rounded 10 centimetres in diameter with a cut surface that of a soft fibro-adenoma. *Histology* (Figs 62-64)—The tumour is a fibro-adenoma with intra-canalicular and peri-canalicular patterns in about equal proportions. The connective tissue is of moderate cellularity in most parts, and some mitoses are seen in the cells. Islands of adipose tissue cells have been incorporated in the peripheral parts of the tumour (Fig. 64).

and their sarcomatous conversion. The experiments prove conclusively the correctness of the view long held by many histopathologists, that the connective tissue component is not merely a stroma to the epithelium but possesses neoplastic properties of its own, i.e. the tumours are genuinely mixed tumours properly designated "fibro adenoma" when benign and (usually) "adeno-sarcoma" when malignant. In the mammary fibro adenomas of dogs, sarcomatous change may

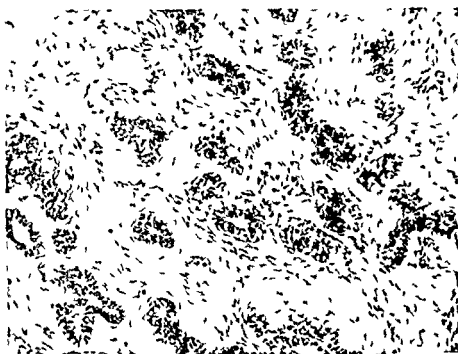


FIG 62—Case III Giant fibro adenoma ($\times 120$)

supervene in the metaplastic bone which the tumours often contain, and ossifying metastases may develop. Schlotthauer and Thurber described an unusual example of osteogenic sarcoma of a dog's breast with osteoid metastases in lymph nodes, lungs, heart and kidney.

DUCT PAPILLOMA AND PAPILLARY CYSTADENOMA

Papillary growths of the breast like those of most other regions, cannot be sharply separated into benign papillomas and papillary carcinomas. All transitions occur between solitary or multiple localized slowly growing highly organized papillomas of main ducts, and poorly organized active papillary growths associated with, and showing obvious transitions to, invasive carcinoma. The present section deals only with the former, the endless permutations between this and the latter can be left to the reader's imagination.

(a) Age and sex incidence

Most simple papillomas are seen in young women, they are rare in children or in subjects over 55 years old. Papillomas of the male breast are extremely rare.

opinion was that an old fibro adenoma had long been present and that carcinoma and sarcoma had supervened in it , and this seems the most likely interpretation



FIGS 60 and 61 —Case II Giant fibro-adenoma ($\times 120$)

Chapter 6 discusses the interesting way in which study of the transplantable fibro adenomas of rats has shed light on the composite nature of these growths

multiple, and that transitions from cystic hyperplasia to papilloma formation could often be traced. Single papillomas were usually in the main ducts near the nipple. Multiple papillomas were usually unilateral, but occasionally bilateral, they might be very numerous—150 or more, and they might affect the whole extent of a duct and its tributaries. Cheate and Cutler aptly likened this condition to papillomatosis of the colon, both as regards the wide extent of the epithelial field affected and the proneness of the papillary growths to become carcinomatous.

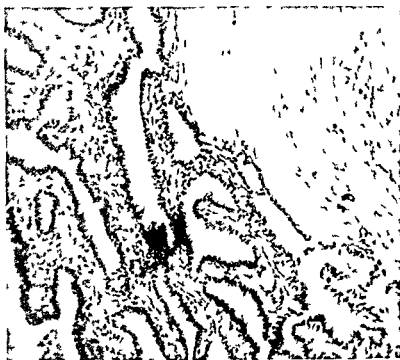


FIG. 65—Multi radicular papillary growth in a cystic duct ($\times 120$)

These observations have an obvious bearing on surgical treatment, they support the view that mastectomy is preferable to local excision of papillomas or papilliferous cysts. When local removal only is undertaken, the surgeon unaware of the pathological state of the rest of the breast, not seldom leaves behind a field of tissue of great or small extent in which similar or more serious neoplasia may manifest itself later. The regular performance of mastectomy—not necessarily the radical operation—for duct papillomas which appear clinically to be solitary and localized may sacrifice some breasts needlessly but it will certainly save other patients from the subsequent recurrence of papillomas or of carcinoma.

(d) *Structure*

Duct papillomas may be sessile or stalked, and the stalked ones may be uni radicular or multi radicular more often the latter. Uni radicular growths may have a simple villous structure, but fenestrated or reticular formations are more common (Fig. 65). Simple distension of part of a duct by a single growth is less frequent than the formation of irregular papilliferous clefts and cysts.

'Papillary cystadenoma' is a name sometimes applied to the latter condition

(b) *Papillomas in animals*

The only animals to show mammary papillomas frequently are dogs in which papillary growths usually along with cystic changes, fibro adenoma or carcinoma are quite common. Feldman mentions papillomas of the teat ducts of cows



FIGS 63 and 64—Case III. Giant fibro-adenoma ($\times 170$)

(c) *Site and mode of origin*

Clellie's studies of whole breast sections revealed that duct papillomas were present more frequently than clinically suspected that they were often

That during recent years there has occurred a real increase in the incidence of breast cancer in Great Britain and the United States of America, independently of the increasing average age of the population, will be pointed out below when age incidence has been discussed

(b) *Clinical and pathological records*

Sufficiently large series of unselected hospital cases show rough general agreement with mortality statistics as regards the relative frequency of mammary, uterine and other common tumours. Thus, the Annual Report of the British Empire Cancer Campaign for 1940 contains a review of 7,872 pooled cases of malignant disease of both sexes from London hospitals, these included 1,345 cases of mammary cancer and 639 cases of uterine cancer, a ratio of approximately 2 to 1. My series of 1 060 necropsy cases of carcinoma (Table V, Chapter 5) included 92 cases of mammary carcinoma and 49 cases of uterine carcinoma—again a ratio of about 2 to 1. The total number of female cases in my series was 425 so that carcinomas of the breast and uterus constituted respectively about 22 and 12 per cent of all female carcinomas, while carcinomas of the large intestine and of the stomach numbered 76 and 70 cases (18 and 16 per cent) respectively. Mammary carcinoma was thus the commonest malignant growth in women.

For populations without proper mortality statistics, clinical and pathological records are the only useful means of estimating the relative frequency of breast cancer and other tumours. Amongst the best studies of this kind are those of Nath and Grewal, in India. These showed that, while mammary, uterine and other cancers varied in their relative proportions in different districts and racial communities pooled figures showed a decided preponderance of uterine tumours. Cancer of the female genitals (mainly of the uterus) constituted 36.5 per cent, and cancer of the breast 24.2 per cent of all female cancers, in Hindus the percentages were 39.0 and 22.4, in Mohammedans 26.3 and 30.5 and in other castes 35.4 and 26.1. These figures are borne out by those of Khanolkar of Bombay, who, in a series of 2,880 microscopically verified cases of carcinoma, saw 300 cases of carcinoma of the cervix of the uterus and 159 cases of carcinoma of the breast, the numbers of cases of these two diseases in Hindus were 229 and 75 respectively, in Moslems 20 and 23, and in Parsees 14 and 27. Quinland and Cuff's collection of 300 cases of carcinoma in negroes included 112 of the uterus and 64 of the breast.

(c) *Sex incidence*

In England and Wales in 1938, there were 7,218 female deaths and 60 male deaths from cancer of the breast. In Victoria, in the decade 1933-1942, 2,518 women and 26 men died of this disease. Many other recorded series also, e.g. those collected by Hoffman, have shown breast cancer in females to be about 100 times commoner than in men. The properties of male mammary carcinoma are described later.

(2) *Age incidence*

(a) *Ages at death*

The mortality figures of England, United States of America and many other countries show closely similar age distribution curves for mammary cancer.

Sessile multiple and irregularly cystic growths are more likely than those of a simpler structure to be associated with or to show transitions to carcinoma

CARCINOMA OF THE BREAST

(1) Frequency

(a) *Mortality rates and race incidence*

Because the diagnosis of mammary cancer in its late stages is in most cases obvious the mortality figures of most civilized countries may be accepted as fairly reliable. Its frequency as a registered cause of death differs decidedly in different countries and the differences are too great to be accounted for by diversity of age and sex composition of the populations (Table I)

TABLE I
MORTALITY RATES FROM BREAST CANCER IN VARIOUS COUNTRIES IN 1930 (DESCENDING ORDER)
ALONG WITH BIRTH RATES 1930 AND 1910
(From Bogen 1935)

Country	Breast cancer		Birth rates per 1 000	
	Death rates per 100 000 females	Percentage of cancers	1930	1910
England and Wales	29.2	19.1	16.3	23.8
Scotland	23.4	15.0	19.5	26.1
Denmark (urban)	22.6	17.3	18.7	25.6
New Zealand	22.4	20.0	18.8	26.0
Switzerland	21.2	11.0	17.2	23.9
Netherlands	19.3	13.8	23.1	28.2
U.S.A.	17.6	16.1	18.9	24.9
Australia	16.5	17.2	19.9	28.1
Ireland	16.0	16.0	20.2	22.6
Norway	14.5	7.4	24.5	25.3
Canada	11.5	17.6	24.5	26.6
Italy	6.0	10.0	26.2	31.7
Spain	3.6	7.0	29.0	31.2
Ceylon	3.6	7.6	39.0	38.1
Japan	1.8	3.0	32.4	34.1
Chile	1.2	2.0	39.8	37.0

Whereas in the earlier years of the present century deaths from uterine carcinoma exceeded those from mammary carcinoma in England and Wales, United States of America, Australia, etc. (see Chapter 31) the reverse now obtains. Thus, of 35 913 female deaths from cancer in England and Wales in 1938, 7 218 (20.1 per cent) were from mammary cancer and 4 519 (12.6 per cent) from uterine cancer. So also in Victoria in the decade 1938-1942 there were 12 428 female deaths from cancer, of which 2 518 (20.3 per cent) were from mammary cancer and 1 656 (13.3 per cent) from uterine cancer. In English and Australian women the recorded deaths from mammary carcinoma exceed those for every other organ including the stomach. In many European countries, most notably the Scandinavian countries and Holland, recorded deaths from gastric cancer greatly exceed those from mammary cancer. The remarkably low death rates recorded for mammary cancer in Italy, Spain, Japan and Chile merit further study.

breast cancer to total cancer deaths has also shown an upward trend, e.g. in U.S.A. this rose fairly steadily from 7.3 per cent in 1900 to 9.5 per cent in 1930 (Bogen), and this in spite of the fact that, while improved diagnosis must have caused an increase in registered deaths from internal cancers, breast cancer could have shared but little in this improved diagnosis. It appears clear then that there has been a real increase in the prevalence of breast cancer, quite apart from its increase because of ageing of the population.

(4) Spontaneous or experimental mammary carcinoma in animals

Mammary carcinoma is of course very frequent in mice, in which, by selective inbreeding, strains of either high cancer or low-cancer incidence have been obtained. The experimental study of breast cancer in mice has been outlined in Section IV of Chapter 4. Bonser (1945), studying the evolution of mouse mammary cancer, found that this, like human cancer, arises gradually and multifocally, but that it usually begins in the acini and that the milk factor acts mainly on the acini. This difference from human cancer, which usually begins in the ducts, raises the question whether a milk factor exists in the human subject.

Dogs frequently develop carcinomas of the breasts (see Chapter 6), and these show many points of similarity to human tumours. They often supervene on cystic hyperplasia and all transitions between this and papillomas and carcinomas are seen. Multifocal origin in one or several breasts often occurs. In a lactating dog's breast, Dawson (1935) saw lactation in a papillary carcinoma. Carcinomatous change in fibroadenoma is not rare. Study of the reproductive and lactational history of dogs with breast tumours is needed.

Carcinoma of the breast is not common in other mammals, but occurs in rats, cats, horses, swine, cows, sheep, rabbits and guinea pigs.

(5) Reproductive and lactational history in relation to mammary carcinoma

Since the breast is subject to hormonal control related to sexual and reproductive functions, on *a priori* grounds we might suspect disturbances of these functions to play a major part in the genesis of breast cancer. The results of much statistical and some experimental work have left no room for doubt that this is indeed the case. Only some of the evidence on this question can be referred to here; for further details see the classical papers of Janet Lane Claypon (1924, 1926 and 1928), and the confirmatory papers of Wainwright and Bogen.

(a) Marital state

It has long been recognized that single women are more liable to mammary cancer than married women. The mortality rates in England and other countries show an excess of deaths among the unmarried when due regard is paid to the proportion of single women in the general population. Lane Claypon's figures from the surgical literature (1924) showed that in England 15 per cent of the female population over 40 years of age were single, but 22 per cent of the breast cancers were from single women; in America the corresponding figures were 8 and 18; in Denmark 14 and 30. The Registrar General's analysis of deaths in 1930-32 showed the death rates of mammary cancer to be markedly greater for single than for married women in all age groups over 35.

Representative of these are the figures in Table IV, Chapter 5. These show that fatal mammary cancer is infrequent under the age of 35 that a rapid rise in the number of deaths occurs in the fifth decade and is maintained in the sixth, that more than half the total deaths take place between 45 and 65 and nearly three-quarters of them between 45 and 75 and that the mortality rates for people of different ages show a continuous rise from youth to old age.

(b) Clinically recorded ages

The studies of Lane Claypon, Wainwright and others have shown that distribution curves of clinically recorded ages—i.e. ages of operation or of onset of symptoms—attain their peak at ages 5 or more years earlier than the mortality curves. The peak occurs early in the sixth decade or in some series (e.g. that of Pack and Le Fevre) near the end of the fifth decade. The difference between the curves for fatal and clinical series in this respect is accounted for by the mean duration of about $3\frac{1}{2}$ years for untreated cases and the markedly prolonged average expectation of life from adequate surgical treatment especially in early cases. (See Lane Claypon.)

Mammary cancer is rarely seen in patients less than 30 years old, but most surgeons and pathologists will recall instances. Velpeau saw the disease in a girl of 17 and in several other women under 30 and more recent records of such cases include those of Wildbolz and of Sears and Schlesinger who reported a carcinoma in a child of 10. My 92 necropsy cases included 2 women under 30 aged 23 and 29. Haagensen and Stout recorded 18 patients under 30 years of age, the youngest 22.

(3) The increase of mammary cancer

The effect of changes in the age distribution of populations on the incidence and age distribution of mammary cancer is well shown in Table II.

TABLE II

TREND OF DEATHS FROM BREAST CANCER IN THE U.S. REGISTRATION STATES OF 1910
(From Bogen 1935)

	1911	1920	1930
Population - - - - -	48 295 860	56 080 552	66 442 606
Deaths from breast cancer - - - - -	3 610	4 900	7 409
Rate per 100 000 (all ages) - - - - -	7.5	8.8	11.2
(15-44) - - - - -	2.9	3.1	3.6
(45-64) - - - - -	22.1	25.6	34.0
(over 65) - - - - -	49.8	55.0	61.6
Percentage of population over 45 - - - - -	20.9	24.0	25.6
Percentage of breast cancer over 45 - - - - -	80.6	82.7	84.4

This table shows that in the United States of America (and the same applies to England and many other countries) the crude mortality rate of breast cancer has risen markedly during recent years and that this rise is due in large part to the ageing of the population. That it is not wholly due to this however is shown by the upward trends of the standardized or age specific rates also. The ratio of

Similar statistical studies of the suckling habits of the Japanese, Chilian, Spanish, Italian, and other women with relatively low incidences of breast cancer, are needed

That premature weaning can engender breast tumours in mice and rats is shown by the experimental results of Bagg and others cited in Chapter 4

(e) The social distribution of cancer

The Registrar General's figures of cancer deaths in England and Wales (1938) indicate a definitive class gradient for mammary cancer. For this purpose each occupation was assigned to one or other of five descending social classes, and married women were grouped according to the social class of their husbands. Expressing the cancer mortality in each class as a percentage ratio of the general average that for cancer of the breast in married women showed a progressive decrease from Class I to Class V as follows, 138, 116, 103, 84, 82. Among single women the class gradient for breast cancer was less pronounced. In general then, women of the upper social classes in England are decidedly more subject to mammary cancer than those of the lower classes. It is quite probable that this is due to reproductive and lactational differences, as already suggested in the preceding section, the upper classes living less "natural" lives as regards reproduction and lactation.

(f) Conclusions

From the foregoing discussion the main facts to emerge are

- (i) Single women are more liable than married women to develop breast cancer
- (ii) The liability to breast cancer in child bearing women is inversely related to fertility, and communities with a low (and especially a falling) birth rate show a high rate of breast cancer
- (iii) There is evidence, statistical as well as experimental, to show that failure to suckle, premature weaning and possibly other errors of lactation play a part in the genesis of mammary cancer
- (iv) Women of the upper social classes in England are more liable to breast cancer than those of the lower classes

It seems safe to conclude then that the women least liable to mammary cancer are those who have borne and normally suckled several children, while the most liable are those who have not borne children, or who, having borne children have failed to suckle them. Thwarted reproduction and thwarted lactation predispose to cancer, normal reproduction and lactation are the prophylactics. With good reason we may strongly suspect that the high and increasing prevalence of breast cancer in the Western civilized peoples is related to the "unnatural" reproductive life of a large proportion of the people.

(6) Heredity and mammary carcinoma

It is possible by close inbreeding to obtain strains of mice of either very high or very low incidence of mammary cancer, but these results are not generally applicable to human communities in which such close inbreeding rarely occurs. Nevertheless, as mentioned in Chapter 5, there is some statistical evidence that the incidence of mammary cancer in female relatives of patients with mammary

(b) *Menstrual history*

Careful comparisons of large series of cases of mammary cancer with proper control series of non-cancerous subjects (Lane Claypon 1926, Wainwright, 1931) showed no significant difference with respect to the age of onset or cessation of menstruation the total duration of menstrual life or disturbances of the menstrual cycle or the menopause. Bonser (1935) observed that the incidence of breast tumours in mice was not demonstrably related to the characters of the oestrous cycle.

(c) *Fertility*

Lane Claypon's comparisons of cancerous and control series of married women showed an unmistakable difference of fertility. Even when allowance was made for cases in which the disease itself may possibly have diminished child bearing capacity, it was found that women who ultimately developed mammary cancer bore 22 per cent fewer children than the control cases. In the control and cancerous series the average numbers of viable children per married woman were 4.97 and 3.53, a ratio of 1.4 to 1. Wainwright's American series showed a ratio of 2 to 1. The average age at marriage was also significantly lower in the control series than in the cancerous series, in both England and U.S.A.

Confirmation of the inverse relationship of fertility and the liability to mammary cancer is afforded by Bogen's observation of a striking parallelism between low birth-rate and high breast cancer rate. Thus England, which in 1930 headed the list for mortality rate from breast cancer, had a birth rate of 16.3 per 1,000, while at the bottom of the list were Japan and Chile with very few breast cancers and birth rates of 32.4 and 39.8 respectively. Moreover, and perhaps even more significantly, countries high in the list of breast cancer showed a diminishing birth rate between 1910 and 1930, e.g. in England from 23.8 to 16.3, while countries with little breast cancer showed no great changes in their relatively high birth rates between those years, e.g. Japan's birth rate in 1910 and 1930 were 34.1 and 32.4, and Chile's 37 and 39.8. A similar inverse relationship obtained between breast cancer rates in the various States of U.S.A. in 1930 and their birth rates in 1900. Bogen concluded from these and other observations that child bearing and lactation constitute a natural protection against the subsequent development of breast cancer.

(d) *Lactation*

Many statistical and clinical workers have laid stress on errors of lactation as a cause of breast cancer. Thus Leaf (cited by Lane Claypon 1924) in a careful analysis of 100 cases of breast cancer found lactational errors in the majority. In her 1926 report Lane Claypon found that complete failure to suckle and the habit of suckling for a very long period were both more common in the cancer series than in the control series. Thus in the control series mothers failed to suckle 7.4 per cent of their children, while in the cancer series 14.6 per cent of the children previously borne had not been suckled. In her 1928 report on a further series of cancer cases, Lane Claypon found a history of failure to suckle in an even higher degree, namely for 19.1 per cent of the children. In Wainwright's American series 28.2 per cent of married women and widows with mammary cancer had never lactated, while the percentage in the control series was 15.7.

the lumina of the ductules are either reduced by the bulky epithelium or enlarged into small or large cystic spaces. A frequent type of lining seen in cystic structures consists of large eosinophil epithelial cells. This type of epithelium, which has been thoroughly studied by Dawson (1932), has often been regarded, erroneously, as sweat gland tissue. It is present in almost all cystic breasts and in many cancerous breasts also, but there is no evidence that it is ever the origin of carcinoma. Cheatle and Cutler regard this type of epithelium as always of acinar origin, and hold also that all large mammary cysts arise from acini. I join Dawson in dissenting from this view, I am unable to distinguish as sharply as Cheatle does between duct and acinar structures in cystic hyperplasia. In my experience, eosinophil epithelium can appear in either acini (ductules) or ducts, and large cysts can develop from either. Microscopically, the fibrosis accompanying the epithelial hyperplasia consists in the earlier phases of rather loose textured fairly cellular tissue but around older atrophic epithelial structures and cysts it becomes more densely fibrous. Increase in the periductal elastic tissue is frequently present. Inequalities in the density of the connective tissue, along with cysts and the more bulky foci of hyperplastic epithelium, give the breast its "lumpiness". Collections of lymphocytes and other inflammatory and phagocytic cells are not infrequent in cystic breasts, but these are secondary to degenerative changes.

(c) *The nature of cystic hyperplasia*

It is now generally accepted that 'chronic mastitis' is a misnomer and should be discarded. Cystic hyperplasia is clearly due to disordered hormonal control of the breast in which oestrogen excess appears to be the principal factor. This is no place to consider at length all the evidence for this; it must suffice to recall that the structure and function of the breast depends on hormonal (especially ovarian) control, to point to the structural changes just described which are clearly non-inflammatory and essentially hyperplastic in character, and to note that the changes of cystic hyperplasia as seen in the human breast can be reproduced experimentally in animals by oestrogen excess (Buttrows Bonser).

(d) *Carcinomatous change in cystic hyperplasia*

Any competent pathologist who has examined a considerable number of surgically removed breasts will find it difficult to remain patient with those surgeons who deny the pre-cancerous potentialities of cystic hyperplasia. This denial is based on two misconceptions. One of these is due to the persistent use of the fallacious term 'chronic mastitis', under which many surgeons continue to group all lumpy breasts irrespective of their histopathology. Hence as Cheatle points out they fail to distinguish the innocuous non-cystic lobular type of hyperplasia ("mazoplasia" or "adenosis") which is frequent in adolescents and young adults and which often resolves, from the permanent cystic type of hyperplasia which develops usually after the age of 30, and is "a lesion of great menace". The other cause of disagreement between surgical and pathological opinion regarding the pre-cancerous proclivities of cystic hyperplasia is failure to distinguish between clinical and pathological diagnosis of this condition. Many women with cancerous breasts give no history of any clinically detected previous breast disease, yet examination of the excised organ shows widespread hyperplasia and

cancer exceeds that in the general female population, nearly ten fold in Dutch women, according to Wassink

There are seen occasional instances of "cancer families" in which several sisters or other near relatives suffer from mammary carcinoma. Said Velpeau in 1853, "I have seen families in which three sisters daughters of one mother who had died of cancer of the breast, were attacked between the ages of 30 and 40 years with cancerous tumours in the same situation." Surgeons of to day encounter similar families (Handley, 1938, Wood and Darling, 1943). In the family reported by Wood and Darling cases of bilateral mammary cancer occurred in four generations, including three sisters in one generation the growths appeared at an average age of 32, i.e. earlier than usual and one patient in the fourth generation developed the disease at the age of 18.

(7) The relationship of carcinoma to cystic hyperplasia

"Chronic cystic mastitis"—the misnomer most commonly used by surgeons, Brodie's "benign cystic disease", Schimmelbusch's disease, "Reclus's disease", Aschoff's "cystic mastopathy", Pribram's "polycystic breast degeneration", Cheate's "cystiphorous desquamative epithelial hyperplasia"—these are some of the synonyms which have been applied to the variants of a change which is sufficiently designated by the simple name "cystic hyperplasia". Because cystic hyperplasia of the breast is a frequent precursor of carcinoma, it is necessary to summarize briefly its main characters. For further details consult Keynes, Charteris, and Cheate and Cutler (1931).

(a) *Naked eye appearances of cystic hyperplasia*

Common to all forms of the disease are visibly increased fibrous tissue, the presence of cystic spaces large or minute and irregularities of consistency apparent to the palpating finger and visible on the cut surface of the tissue. These irregularities are due to cysts, to unequal fibrosis, to hyperplastic enlargement of groups of lobules, or as the microscope sometimes unexpectedly shows to early multifocal carcinoma. The changes may be universal throughout the breast or may affect only a part or parts of it. Cysts may be large, and single or multiple, or they may be tiny, scattered and inconspicuous. Their contents may be clear and watery or thick and creamy, that of the large cysts often being clear, while that of small cysts and dilated ducts is often creamy and expressible from the cut surface like worm casts.

(b) *Microscopical changes in cystic hyperplasia*

These involve the ducts, acini (better called "ductules", as Dawson points out) and connective tissues. The small terminal ducts are more affected than the large main ducts. The duct epithelia show proliferation, desquamation especially of large pale degenerating cells resembling colostrum corpuscles, banking up of cells in masses, and papillary formations, and the duct lumina are distended by the desquamated cells and by cell debris. Epithelial hyperplasia in ductules distends these increasing their bulk and so causing their packing together in prominent lobules around the small terminal ducts. The multiplying epithelial cells are enlarged, packed together and may assume papillary formation, and

The possibility that the relationship between cystic hyperplasia and carcinoma of the breast may be due in part to the formation of carcinogenic substances in retained secretions has been suggested by Cheatele, Keynes, Charteris, Cappell, and myself (in Section IV of Chapter 4)

The following personally studied cases illustrate the supervention of multifocal carcinoma in cystic hyperplasia, as well as other important features of mammary carcinoma (See also Figs 68-70)

Case IV—A single woman of 26 had had a lump in the upper outer quadrant of the right breast since the age of 12. It had remained unaltered until recently, when following a blow on the breast it had increased in size and become painful. Examination showed a hard area 2.5 centimetres in diameter adherent to the skin. Radical mastectomy was performed (September, 1937). An area of carcinoma 3 centimetres in diameter lay in the peripheral part of the upper outer quadrant. At another part of the periphery there was a second carcinomatous area 9 millimetres in diameter. The remainder of the breast showed firm but pliable fibrosis and many scattered small nodular areas and small cysts. From naked-eye examination this tissue was not thought to be cancerous but to be the seat of lobular and fibrous hyperplasia. To our surprise however microscopic study showed that the entire breast contained focal or diffuse areas of early carcinoma clearly arising from and replacing previously hyperplastic lobules or ducts (Fig 66). The two areas of macroscopically obvious carcinoma were clearly only the most advanced and oldest regions of neoplasia in a breast which was in process of similar change *in toto*. In September 1939 the patient complained of pain in the back and skiagrams showed partial destruction of the 7th dorsal vertebra. Deep X ray therapy was followed by improvement, and the patient married in 1940. In January 1941 a 3 months' pregnancy was terminated for prophylactic reasons. In March 1941, pains in the back were still present. The left breast appeared normal.

Case V—A married woman aged 42 the mother of 2 children had noticed a lump in the left breast for 6 weeks. Examination showed a mass $5 \times 4 \times 1.5$ centimetres in the upper inner quadrant unattached to skin or muscle and slight general lumpiness of the rest of the breast. The right breast also was 'knotty, with chronic mastitis'. In June 1936 simple mastectomy of the left breast was performed. Sections showed active carcinoma supervening on widespread hyperplastic changes. X ray therapy was given and in November 1936 the patient remained well. In November 1937 she complained of a lump in the right breast noticed for 2 weeks. Examination showed chronic mastitis with 7 cysts in upper outer quadrant. The treatment adopted was simple mastectomy followed by deep X ray irradiation. Section of the breast showed it to consist largely of plant fibrous tissue containing many small cysts and dilated ducts with milky contents and many discrete hard shotty patches. Sections from various parts showed cystic hyperplasia with multiple early carcinomatous areas.

Case VI—The seemingly ill advised haphazard treatment of this patient was due to her having attended 4 different clinics at 2 different hospitals without disclosing this to the several doctors concerned. She was a sterile married woman of neurotic type who first attended hospital in 1935 at the age of 31, complaining of a lump in the right breast. This was a well defined rounded mass 1.5 centimetres in diameter which was diagnosed 'fibro adenoma' and was enucleated. Although naked-eye section of the tumour appeared to confirm this diagnosis microscopic study unexpectedly disclosed a localized carcinoma. The patient then transferred herself to another hospital where in a gynaecological clinic she received prolonged intermittent treatment with oestrogenic hormones. In November 1939 the left breast was amputated and sections showed widespread cystic hyperplasia with early multifocal carcinoma. In June 1941 chronic mastitis of the right breast was diagnosed. In 1942 this breast was removed and also showed extensive cystic hyperplasia and multiple areas of well-established carcinoma. There were no signs of recurrence in January 1943.

sometimes multicentric carcinomas which were undetected clinically For every case in which a *clinical* diagnosis of cystic hyperplasia antecedent to carcinoma has been made there are a score in which a *pathological* diagnosis of this sequence is clear from adequate examination of the amputated breast (Lane Claypon, 1926)

The danger of cystic hyperplasia in the middle aged woman has been fully discussed by Cheatele (1920 and 1925), Kevnes Lane Claypon Charteris, Cheatele and Cutler Handlev, Warren, Muir Dawson (1943) and many others The proportion of cancerous breasts which show definite transitions from hyperplastic changes to carcinoma is estimated variously by different workers, Cheatele and Cutler placed it at 20 per cent but others including myself think this is an underestimate For reasons already given it is impossible to determine even approximately what proportion of breasts with cystic hyperplasia may become cancerous

Carcinoma supervening on hyperplasia is often multicentric or diffuse in origin arising from extensive reaches of one or more ducts or even from the entire breast Sometimes such tumours are bilateral and should a middle-aged woman with cystic hyperplasia of both breasts develop carcinoma in one, the risk of carcinoma supervening in the other also is great enough to justify local mastectomy of the second organ Dogs sometimes show simultaneous carcinoma of all mammae with striking examples of transition from widespread cystic hyperplasia to papillomatous growths and carcinoma

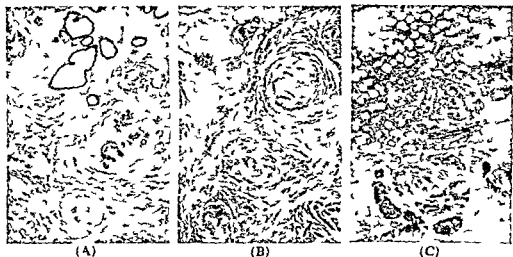


FIG 66—Case IV A B and C are from widely separate parts of the breast ($\times 35$)

It is not denied that some breast cancers are of localized origin and unaccompanied by significant changes in other parts of the organ But purely local growths are much fewer than would appear from clinical examination only Further microscopical examination of only one or two small sections of areas of obvious growth is inadequate to reveal the relationship under discussion and must lead to false conclusions regarding it The more thoroughly the pathologist examines amputated breasts the more often he will discover the presence of cystic hyperplasia in association with carcinoma and of clear transitions from one to the other

duct obstruction might sometimes be causative in the human breast also, or might precipitate neoplastic change in breast tissue already prepared for it

Suppurative mastitis does not predispose to cancer, but transient non suppurative mastitis may possibly do so (Lane-Claypon) Tuberculosis and carcinoma occasionally coexist in the breast (Bundschuh), but the association is probably fortuitous It is noteworthy that mammary tumours are very rare in cows, in which tuberculosis and other kinds of bacterial mastitis are common

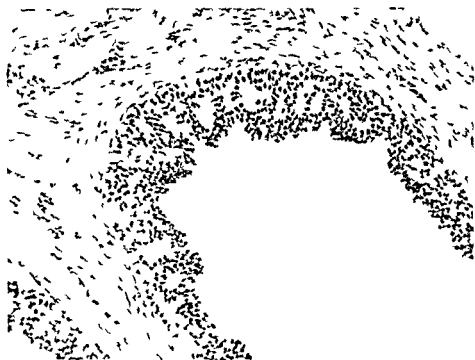


FIG 67 —Early intra ductal carcinoma in a large duct ($\times 120$)

(9) Site and mode of origin

That breast carcinomas often arise from more or less extensive fields of prepared tissue will be clear from the preceding pages and from Chapter 7 Cheate and Cutler grouped the tumours according to their origin as follow

(i) *Carcinoma arising in the nipple*—This comprises tumours of the main ducts in the nipple, and those of its epidermal surface (see Paget's disease)

(ii) *Carcinoma arising in a localized part of a large duct*—The most frequent form is papillary carcinoma, which may long remain confined within the duct as 'papilloma' or papillary cystadenoma before invasive properties appear

(iii) *Carcinoma arising in a main duct and all its tributaries and acini*—This forms a large irregular pyramidal growth with its base towards the periphery of the breast and its apex towards the nipple It often shows all stages of carcinomatous change in progress and is a very fatal type

(iv) *Carcinoma arising in terminal ducts and acini*—This is the common peripheral type of growth

(v) *Carcinoma arising diffusely throughout most or all of the breast or of both breasts*—This is a rare very fatal type producing a small firm breast with no single palpable focus of tumour sometimes accompanied by Paget's disease

Case VII—A woman aged 43 had noticed a lump in the right breast for 3 weeks. It was excised locally; sections showed fibro adenomatous nodules amidst areas of extreme hyperplasia and one small focus of intra duct carcinoma. Simple mastectomy was then performed and sections showed generalized cystic hyperplasia but no other areas of definite growth. A year later there was some general enlargement of the left breast and enlarged right axillary glands were felt. Left mastectomy was performed and the right axilla was cleared. The breast showed generalized cystic hyperplasia; the axillary glands showed large deposits of spheroidal-cell carcinoma.

Case VIII (Mr John Kennedy's case)—In November 1941 a single woman aged 47 consulted her doctor with signs of a thyroid adenoma and thyrotoxicosis and also a clearly carcinomatous mass in the right breast with enlarged axillary lymph glands. Radical removal of the breast was performed; section showed an area of obvious carcinoma 4 centimetres in diameter and cancerous deposits up to 2.5 centimetres in diameter in the lymph glands. Microscopic examination confirmed these findings and showed also areas of cribriform carcinoma in the ducts in other parts of the hyperplastic breast tissue. In December 1942 a lump appeared in the left breast which was removed. Section of the fixed organ showed widespread fibrous change with scattered small cysts; a deep-seated area of carcinoma 2.5 centimetres in diameter and at the inner periphery of the hyperplastic breast remote from the carcinoma a well defined encapsulated fibro adenoma 1.5 centimetres in diameter. These findings were confirmed microscopically. In February 1944 a small nodule was excised from the scar on the right side and was found microscopically to be carcinomatous.

Case IX (Mr A. J. Trinca's case)—The patient had tumours palpable in both breasts and bilateral radical removal was performed. Sections after fixation showed widespread hyperplasia of moderate degree in both breasts and 3 separate tumours as follows:
R. Breast (1) An irregular mass 2.5 centimetres in diameter slightly adherent to the skin at the lower periphery; microscopically spheroidal-celled and adenocarcinoma.
 (2) A well defined freely mobile mass 2.5 centimetres in diameter in the inner periphery at first thought to be a simple fibro-adenoma but microscopically a focus of spheroidal-celled carcinoma accompanied by several small fibro adenomatous foci.
L. Breast (3) An irregular hard mass in the upper outer periphery adherent to the pectoral fascia; microscopically densely scirrhous spheroidal-celled carcinoma. No tumour deposits were found in lymph glands on either side.

Case X (Mr W. D. Upjohn's case)—In 1937 a sterile married woman had chronic mastitis which was symptomatically improved by administration of stilboestrol. In 1943 a small wart like growth appeared on the right nipple and was removed by diathermy by a dermatologist. This recurred a few months later and was again removed by diathermy. Subsequent healing was imperfect and a surgeon was consulted. He found evidence of bilateral chronic mastitis and some enlarged glands in the right axilla and advised removal of the right breast and axillary contents which was carried out in October 1944. *Macroscopically* the breast showed a depressed puckered nipple, some thickening of the periductal connective tissues and a few scattered small cysts up to 4 millimetres in diameter but no sign of any tumour. The axillary glands however contained large deposits of obvious growth. *Microscopically* the glands showed large deposits of active spheroidal cell carcinoma with some mucoid change. The nipple area was free of tumour. Many sections of different parts of the breast showed microscopic foci of carcinoma clearly arising multifocally from hyperplastic ducts and widely infiltrating lymphatics; no carcinomatous mass of a size visible to the naked eye was anywhere present.

(8) The relationship of carcinoma to injury and inflammation of the breast

Injury is often blamed as the cause of mammary tumours but in most cases it is clearly only coincidental or serves to draw attention to a tumour already present. However in view of the experimental results of Bagg and others on the part played by injury of ducts in the genesis of breast tumours in mice and rats (Chapter 4) we must admit the possibility that previous injury leading to

structure seen in carcinomas of the breast may be described conveniently in the following order



Figs 69 and 70—Details of the intra ductal growth shown in Fig 68. Note the restriction of the tumour to duct confines, and its cribriform pattern ($\times 80$)

(a) Intra-ductal types of growth—papillary, cribriform, laciform and solid

The four quadrants of the breast are affected with very unequal frequency, the order being—upper outer upper inner, lower outer and lower inner quadrants. This is exemplified by the following grouping of sites in 640 amputation cases recorded by Haagensen and Stout

Cases				Cases			
Upper outer quadrant	-	-	277	Lower half	-	-	15
Upper inner quadrant	-	-	78	Outer half	-	-	35
Centre	-	-	74	Inner half	-	-	5
Lower outer quadrant	-	-	51	Entire breast	-	-	15
Lower inner quadrant	-	-	28	Unspecified	-	-	15
Upper half	-	-	47				

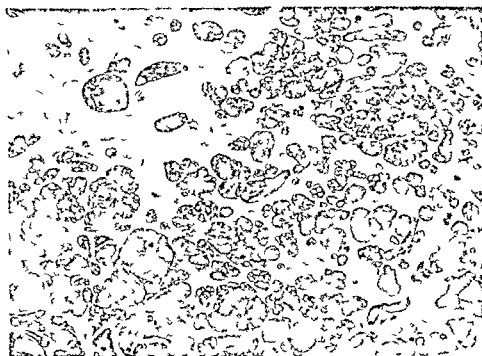


FIG 68 —Intra ductal carcinoma of cribriform type from a woman of 38. At age of 33 an area of cystic mastitis was locally excised she then remained well for 4 years when the growth here depicted was noticed. Four years after mastectomy a recurrent ulcerated growth was present ($\times 8$)

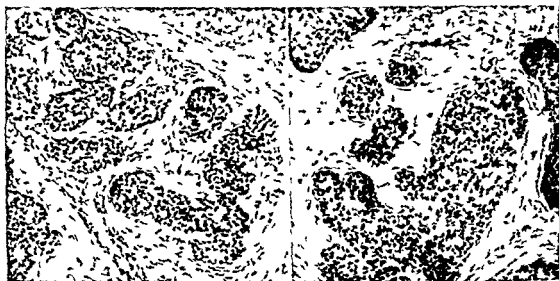
(10) Structure of mammary carcinoma

Carcinomas of the breast show a wide range of microscopical structure—from highly organized papillary or adenocarcinomatous to diffusely cellular anaplastic growths. Quite commonly different parts of one tumour show different structural variants and terms such as 'comedo', 'scirrhous', 'medullary', 'adenoid' and 'simplex' have only locally descriptive not classificatory value. While individual tumours often show predominance of one or another type of structure the structure of a tumour is rarely uniform throughout. Histological subdivisions of mammary carcinoma are arbitrary and, when they are based on single or few sections of each tumour they are often misleading. The main varieties of

These include the following

(i) *Adenocarcinoma*—Usually of simple acinar types, with either scanty or abundant fibrous stroma—less commonly of papillary and cystic types (See also mucoid carcinoma below)

(ii) *Spheroidal cell carcinoma simplex*—Often called also “alveolar” carcinoma consisting of solid clumps or strands of polyhedral cells set in a sponge work of stromal connective tissue (Figs 74 and 75) This tissue may be abundant and dense (‘scirrhus’ carcinoma), or scanty and delicate (“medullary” or ‘encephaloid’ carcinoma)



FIGS 72 and 73—Ductules distended by carcinoma ($\times 120$)

(iii) *Diffuse anaplastic carcinoma*—Diffuse anaplastic carcinoma comprises the most disorderly rapidly growing forms of carcinoma simplex, ranging from the most cellular forms of the previous type (ii) to completely diffuse pleomorphic or spindle-cell growths devoid of any histological signs of epithelial arrangement

It must be insisted again that these types of growth are not entities but merely variants of the entity *mammary carcinoma* and that the more thoroughly tumours are examined, the more often individual tumours are shown to have a range of structure including several of these variants. A broad parallelism obtains between the predominant type of structure of tumours and their prognosis—(i), (ii) and (iii) denoting an ascending order of malignancy, but this is of little value in individual prognosis unless the particular tumour has been examined very completely and has been found nearly homogeneous in structure

(c) *Metaplastic types of carcinoma*

These are not separate types either, but merely variants of the preceding types, showing aberrant differentiation or metaplasia of part of the cancerous epithelium in one or other of two ways

(i) *Mucoid carcinoma*—Mucoid carcinoma shows secretion of mucus in small or large amounts by the cancerous epithelium. Scanty secretion of mucus may be seen only microscopically, in the form of *signet ring cells* each containing

(b) Extra ductal or infiltrative—adenocarcinoma spheroidal cell carcinoma, and diffuse anaplastic types of carcinoma

(c) Metaplastic types of growth—mucoid ('colloid') carcinoma, including signet ring-cell carcinoma and squamous cell carcinoma

(a) *Intra ductal types of growth*

Cheattle's important studies of pre invasive carcinoma, still confined within duct boundaries are readily verifiable by any student of breast pathology. The duct epithelium for short or long distances shows carcinomatous change *in situ*, and the duct lumina become filled and distended by the proliferating cancerous epithelium. The patterns assumed by this intra ductal growth vary (Figs 67-73)



Fig 71—Intra ductal carcinoma in an area of cystic hyperplasia ($\times 60$)

They include papillary carcinoma, not sharply separable from simple papilloma cribriform or laciform carcinoma and solid masses of cells completely occluding the distended ducts. All of these forms of growth may be seen in one breast, and of course may coexist with areas of invasive carcinoma. The so-called comedo carcinoma consists of such intra ductal growths which along with products of degeneration or secretion in the obstructed ducts are expressible from the cut surface of the tumour. Clearly the prognosis of tumours which consist wholly or largely of growth still confined within duct boundaries is much better than that of tumours of predominantly invasive types. But before pronouncing favourably on such cases the pathologist must examine many parts of the diseased breast in search for invasive growth for it is the presence or absence of this which will determine the prognosis.

(b) *Extra ductal infiltrative carcinoma*

Invasive tumours may develop by escape of previously intra ductal growths from their duct confines or may arise *ab initio* from duct or alveolar epithelium. Their structure is protean and variants of all types frequently occur in one tumour.

(a) Spread in the ducts

What appears to be spread of growth within the ducts of the breast results, I believe, almost always, not from invasive extension, but from spread of the cancerous change in the duct epithelium. Appearances clearly attributable to invasion of a duct by investing tumour cells are occasionally seen, but the occupation of long reaches of ducts or of many small ducts by intra ductal tumour, as in Figs 67-73, is due to origin of the tumour *in situ* and not to permeative growth.

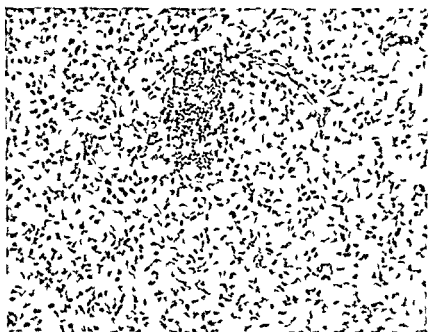


FIG 76—From a lymph nodal metastasis of signet ring-cell carcinoma of breast ($\times 120$)

(b) Lymphatic oedema of the skin

Nelaton is credited with having first used the apt term '*peau d orange*', and Banks (1900) applied the name, 'pig skin' to the same condition. In 1909 Leitch showed that this was a thickening of the corium due to cancerous occlusion of the deep dermal lymph vessels—the pits in the swollen skin being the exaggerated orifices of hair follicles. While most subsequent writers have agreed with Leitch that continuous permeation of the lymphatics by tumour cells was the essential lesion in *peau d orange*, Haagensen and Stout pointed out that embolic extension rather than continuous permeation in the dermal lymphatics probably plays an important part in the early stages. Since 'pig skin' denotes more or less extensive spread by lymphatic channels, it is a bad prognostic sign even when of limited extent, when a considerable fraction of the skin of the breast is affected surgery is never curative.

(c) Satellite nodules and cancer en cuirasse

These are late results of embolic and permeational spread in the dermal and deeper lymph vessels. Extending occlusion of these vessels by growth leads to an extending zone in which embolic dissemination in lymphatics of small calibre is constantly taking place in a centrifugal direction. Each arrested embolus establishes a new focus of growth from which further permeation and dissemination

a globule of mucin these may be few in number and mingled with ordinary spheroidal cell growth, or they may outnumber other cells and give parts of the tumour a slightly translucent gelatinous appearance (Fig 76) When abundant mucus is secreted, this is discharged extra cellularly in large amounts, and typically *gelatinous* or "*colloid*" cancers result It has often been stated that these are relatively favourable in prognosis but this has not been my experience although some of these tumours grow rather slowly in the breast, they are no less productive of metastases than other invasive types of growth Cheate and Cutler also in a thorough study of 10 cases of gelatinous cancer failed to substantiate their supposedly low malignancy Calcification sometimes occurs in the more chronic gelatinous carcinomas as in the case reported by Shore

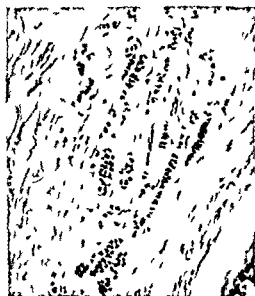


FIG 74 —Scirrhus spheroidal-celled carcinoma simplex ($\times 120$)



FIG 75 —Cellular spheroidal-celled carcinoma simplex ($\times 60$)

(ii) *Squamous metaplasia*—Squamous metaplasia is rarer in mammary carcinomas than might be expected in view of the development of the breast from the ectoderm I saw it in only 5 of 552 surgically treated cases (Figs 77 and 78) It is usually present only in parts of the tumours and is of no special prognostic import Foot and Moore saw an epidermoid carcinoma of the breast with wide spread metastases which also showed squamous cell structure I have examined a breast containing a spheroidal cell carcinoma and showing simple squamous metaplasia in ducts elsewhere

(11) The direct spread of mammary carcinoma

I propose to say little on this subject for the routes of spread have been discussed in Chapter 9 and the details of local spread of breast cancer are of far less importance than its powers of metastasis Certain special points only deserve comment here

Others have shown no special skin lesions, but the tumours have grown rapidly and diffusely in the breast, and have been accompanied by oedema, redness and heat, and sometimes by pain and tenderness. This condition, especially if occurring during pregnancy or lactation, may be mistaken for acute mastitis or abscess, as in Case 332 of my 1941 paper. Taylor and Meltzer have given a good account of "inflammatory" carcinoma.

(12) The metastasis of mammary carcinoma

Metastases from carcinomas of the breast occur frequently and in many and diverse sites. In 45 consecutive necropsies (Willis, 1941), I found metastatic growths in the following situations:

Lymph glands - - -	36 cases (80 per cent)	Thyroid gland -	8 cases
Pleura - - -	19	Dura mater -	7
Peritoneum - - -	6	Brain - - -	7
Pericardium - - -	2	Kidneys - - -	7
Remote, mainly blood borne metastases present in -	33 (73 per cent)	Spleen - - -	4
Lungs - - -	28 (61 per cent)	Intestinal mucosa -	4
Liver - - -	22 (49 per cent)	Pancreas - - -	3
Bones - - -	21 (47 per cent)	Ovaries - - -	3
Adrenals - - -	9	Myocardium - - -	2
		Endometrium -	1

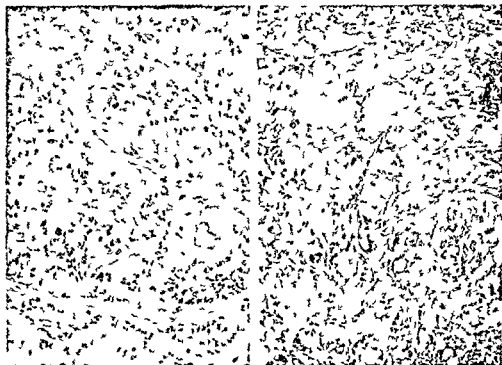
Of course these figures apply to the final stages of the disease. The frequency of metastases in particular sites in earlier stages is difficult to determine, but that they are often present is shown by the disappointing frequency with which, following successful removal of the breast in cases adjudged operable, metastatic growths in various situations subsequently manifest themselves.

(a) Metastases in regional lymph glands

The commonest site of secondary growths from mammary carcinoma is in the axillary group of lymph glands and these growths are established by embolism, not by continuous permeation (see Chapter 10). The frequency of axillary deposits in amputated specimens necessarily varies from series to series according to the criteria of operability adopted. In 622 radical mastectomies with microscopic examination of the axillary glands, Haagensen and Stout found these involved in 385 i.e. 62 per cent. My own experience is in close agreement with this, 280 radical mastectomies I found axillary deposits in 158 i.e. 56 per cent. Dawson (1943) found axillary involvement in 70 per cent of operation cases. As might be expected, the frequency of axillary metastases is related to the known duration of the tumours prior to operation. Thus in Haagensen and Stout's series, axillary deposits were present in 50 per cent of cases of duration less than one month, in 60 per cent of cases of duration between one and six months and in 68 per cent of cases of more than six months' duration. As noted above, about 80 per cent of fatal cases show axillary deposits.

Of all the factors influencing post operative prognosis, the condition of the axillary glands is the most important. Thus in the series reviewed by Lane Claypon 66 per cent of cases with unaffected glands survived for 5 years and 57 per cent for 10 years but when the glands were diseased the percentages were

proceed. Satellite nodules in skin and fasciae are local embolic metastases, which however soon become confluent with one another. In cancer *en cuirasse*, the spread is more diffuse and affects all available tissue interstices as well as lymphatic channels.



Figs 77 and 78 —Cornifying squamous-cell carcinoma of breast from primary growth and axillary metastases ($\times 60$)

Typical cases of widely disseminated skin nodules were carefully studied by Handley (1922) who also reviewed some earlier records. Carnett and Howell saw unusually widespread nodules over the entire trunk, on the limbs, face and scalp, and also in the oral mucosa and vaginal and rectal walls. In cases described by Riehl and by Goldsmith, scirrhous plaques in the scalp were accompanied by loss of hair. Askanazy and Jentzer saw cases in which dermal nodules caused pain and local sensory disturbances, due to close investment of cutaneous nerves by the growths. Newcomb saw deep pigmentation associated with skin nodules, due to vascular proliferation and haemorrhages in and beneath the epidermis.

(d) *Telangiectatic or erysipelatoid carcinoma*

This is a form of mammary carcinoma which besides involving the dermal lymphatics, extensively permeates and disseminates in the small blood vessels of the skin and other tissues. The nodular hyperaemic areas are not necessarily restricted to the neighbourhood of the breast, but may develop also in other parts of the trunk, neck or face, doubtless from metastatic foci. For good accounts of this condition, see Weber and Dawson and Shaw.

(e) *Inflammatory carcinoma*

Some of the cases so designated have been of the 'erysipelatoid' type

practice would certainly obviate many useless operations. In many cases, however, remote metastases will elude even the most thorough clinical search and will not make their presence evident until months or years—even 15 or 20 years—have elapsed.

Secondary tumours in the lungs, present in nearly two thirds of fatal cases, appear usually as scattered discrete well defined growths, less often in the form of miliary carcinomas or of nodular lymph-vessel carcinosis of the lung and visceral pleura. Of course, direct invasion of the parietal pleura from the primary growth or from affected supraclavicular or mediastinal lymph glands may lead to transpleural involvement of the lung or to intrapleural dissemination and effusion.

Secondary tumours in the liver, present in about one half of fatal cases, are nearly always well defined discrete growths, rarely diffuse infiltrations (references Willis, 1934, p. 253). The tumours show no particular distribution in the organ but are scattered indiscriminately in all parts. They clearly reach the liver by the blood stream, and not by epigastric lymphatic channels as suggested by Handley.

Secondary tumours in bones are present in about one half of fatal cases (47 per cent in my series, 52 per cent in Kaufmann's). Contrary to Handley's contention, their distribution does not show any centrifugal relationship to the primary growth, like other metastatic tumours in bones they occur most frequently in those bones which contain abundant red marrow, and most of them are clearly blood borne deposits in this tissue (Willis, 1934, p. 332 and 337-342). Their usual effect on the bone is osteolysis, but dense osteoplastic change is not uncommon. Extensive metastases may be present in bones which appear radiographically normal (Willis, Haagensen and Stout). Metastases in bones may produce the first symptoms of the disease (references, Willis 1934, p. 198, and Trinca and Willis, Case XVI), or they may manifest themselves many years after removal of the primary tumour (Willis, p. 112).

Secondary tumours in the brain are present in about 20 per cent of fatal cases of mammary carcinoma and the most frequent source of metastatic growths in the brain is cancer of the breast. These are usually discrete well defined growths, often multiple, and situated in any part of the brain. Multiple metastases in other organs are present in most cases but a solitary metastasis may be found in the brain only (Willis, 1939). The following case is remarkable for the long period—nearly 15 years—intervening between apparently successful removal of the primary growth and the appearance of symptoms due to cerebral metastases and for the presence of massive calcification in these.

Case XIII—A woman aged 52 was admitted to hospital in December 1934 under the diagnosis cerebral tumour or abscess. She had had ataxia failure of vision headaches and vomiting for 3 months and early papilloedema was present. Examination also showed the healthy scar of previous radical removal of the left breast performed early in 1920. Ventriculography revealed a large filling defect of the left ventricle corresponding to which there was a large area of heavy calcification in the posterior parietal region. Operation (Mr H. C. Trumble) disclosed a well defined partly cystic partly calcified tumour 7 centimetres in diameter this was removed. Microscopical examination showed spheroidal-cell carcinoma with widespread necrosis and calcification. The patient died 1 week after the operation. *Necropsy* revealed tumour deposits in the hilar regions of both lungs and in the mediastinal lymph glands some residual tumour tissue in the operation area of the brain a metastasis 3 centimetres in diameter in the

only 29 and 14 respectively. So also Haagensen and Stout found that when the axilla was clear of disease, the percentage of 5 year clinical cures was 61, but that when axillary metastases were present, it was only 21 per cent.

Careful dissection and microscopic examination are essential to determine the presence or absence of early axillary metastases, clinically impalpable glands may contain metastases and enlarged glands may contain none. Thus in Haagensen and Stout's series microscopical study revealed tumour deposits in 44 per cent of cases in which the clinician believed the glands to be unaffected while no tumour deposits were found microscopically in 15 per cent of cases in which the clinician had believed them to be present. Haagensen and Stout mention a case in which massively enlarged glands measuring up to 3 centimetres in diameter contained no growth and I have seen similar cases. However, glands 2.5 centimetres or more in diameter are rarely found clear of tumour.

Axillary tumours may attract attention long before any abnormality is apparent in the breast. References to such cases are given in my 1934 work (p. 197) and the following are additional examples.

Case XI—A woman aged 52 had noticed an enlarging mass in her right axilla for 2 months. No abnormality of the breast could be detected. The enlarged axillary glands were excised, and were found to be massively replaced by active spheroidal-cell carcinoma. The largest gland measured 6 centimetres in diameter. Radical removal of the seemingly normal breast was performed. There was no growth in the main part of the organ but in the axillary tail close to several remaining cancerous lymph glands there was a small primary carcinoma 1.2 centimetres in diameter.

Case XII—A woman aged 47 had noticed an enlarging mass in the right axilla for 9 months. It was excised and found microscopically to be a greatly enlarged lymph gland replaced by glandular and spheroidal-cell carcinoma. Careful re-examination of the breast then detected very slight *peau d'orange* above and lateral to the nipple but without any palpable tumour the breast was removed. Naked-eye examination disclosed no obvious tumour in any part of the organ which however especially its outer half showed generalized finely nodular thickening. Microscopical study of the nipple area and the lateral parts of the breast showed mild hyperplastic changes with some dilated ducts and microscopic areas of spheroidal-cell carcinoma infiltrating lymphatics.

Spread to the cervical, mediastinal or inguinal lymph glands often takes place in the later stages of mammary carcinoma but rarely, if ever, precedes involvement of the axillary glands. These more remote groups of glands become affected as the result of embolic or permeational spread from gland to gland or retrograde embolic dissemination following occlusion of the axillary lymphatic paths (see Chapter 10). Halsted's operation for the removal of supraclavicular glands has lost favour. Patients with deposits in these glands should certainly be classed as inoperable.

(b) *Metastasis by the blood stream*

In the late stages of breast cancer remote metastases are of course frequent and often widespread as the list given above shows. They are present in about three quarters of fatal cases. The lungs, liver and bones are their commonest sites and the frequency with which such metastases develop following otherwise successful treatment of the primary growths fully justifies Haagensen and Stout's practice of including in their routine examination of every new patient skiagrams of the lungs and of the entire skeleton except the distal parts of the limbs. This

controlled series of cases is necessary. However, from the evidence so far, it seems clear that temporary retardation of growth has occurred in some oestrogen-treated cases.

It has long been recognized that carcinoma of the breast appearing during pregnancy or lactation is often highly malignant and speedily fatal. Dawson's study of 15 cases showed this to be due more to early dissemination than to unusual rapidity of growth of the tumours. These showed a range of structure and differentiation similar to that seen in carcinoma of the functionally quiescent organ, and only a few of them were highly anaplastic, but invasion of the lymphatics or blood vessels of the vascular active breast was often seen, and many of the patients soon died from metastases. However, the exacerbation of growth of some carcinomas of the breast during pregnancy and lactation and their retardation following weaning (as in my Case No. 332, 1941) point plainly to hormonal factors controlling the rate of growth. Future researches in this field will include not only clinical studies but also hormone assays in suitable cases, and the experimental study of the fluctuations of growth of mammary tumours in animals as the result of pregnancy and of the administration of hormones.

(14) Carcinoma of the male breast

Valuable descriptions and reviews include those of Speed, Wainwright, Cheate and Cutler, Gilbert, and Scarff and Smith. The disease occurs with a frequency of only about one hundredth that of cancer of the female breast. The average age of affected males is about 54 years, ages ranging from 12 to 91 have been recorded. Trauma has often been blamed, but is of very doubtful significance.

Gilbert cited the recorded cases in which mammary hyperplasia (gynaecomastia) co-existed with carcinoma of the male breast—an association which was present in 9 of 47 cases in his own series. Villeon (cited by Gilbert) and Burrows have recorded cases of mammary cancer associated with prostatic enlargement. These clinical observations along with the experimental production of carcinoma of the breast in male mice by oestrogens (Chapter 4), strongly suggest that hormonal disturbance is a causative factor in this disease.

Pathology

In structure, growth, metastasis and prognosis, cancer of the breast in males closely resembles that in females. The site of origin of the tumour is seldom far from the nipple, and as might be expected, both ulceration of the skin and invasion of the subjacent muscle and chest wall often occur sooner than in the female breast. Paget's disease is rare. In more than half of the cases, the axillary lymph glands are already affected when the patient first comes under observation, and operability and prognosis are often unfavourable. The commonest sites of remote metastases are lungs, liver and bones.

The two following personally studied cases are notable: the one because the tumour was in an early stage and still confined within the ducts; the other because it was of the rare intra-cystic papillary type.

Case XVI (Dr Norman Freemantle's case)—A man aged 72 had a blood-stained discharge from his nipple and then felt a small mass in the breast. No axillary glands were palpable. Local mastectomy was performed. The thickened tissues beneath the

middle of the cerebellum, and a metastasis 1 centimetre in diameter in the white matter of the right frontal lobe. There were no metastases in any other organs and no sign of recurrent growth in the mammary area. Sections of the original breast tumour were available and comparison of these with sections of the cerebral and mediastinal growths left no doubt that these were indeed metastases of the former.

Secondary tumours in other parts. Accounts of these are given in Part II of my 1934 work, and elsewhere also I have described metastases from carcinomas of the breast in the thyroid gland (1931), and in the intestines (1931). The following case showed clinically prominent splenic and other metastases from an inconspicuous primary growth. (For references to other cases of diffuse metastatic carcinoma of the spleen see my 1934 work p. 287.)

Case XIV—A woman 61 years old complained of anaemia and weakness of 10 months duration and of intermittent diplopia. Examination showed marked pallor, some enlarged cervical lymph glands and palpably enlarged spleen and liver. Both breasts were somewhat nodular to palpation but no definite growth was detected. Test meal showed total achlorhydria but no lesion was visible in skiagrams following barium meal or barium enema. Diagnosis of primary anaemia was made, but section of a gland removed from the neck showed secondary spheroidal-cell carcinoma. *Necropsy* revealed an ill defined area of induration in the right breast which proved microscopically to be a diffusely infiltrating spheroidal-cell carcinoma. The liver was enlarged and studded with secondary growths. The spleen 820 grammes was uniformly enlarged and hard; its cut surface showed ill defined diffuse and confluent patches of white growth resembling the porphyry spleen of Hodgkin's disease—microscopically it showed widespread carcinomatous infiltration. Both adrenals were enlarged by metastatic growths. The inner aspect of the cranial dura mater was studded with many projecting nodules and flat plaques of tumour. Section of the bones was unfortunately omitted. Other organs were normal.

The following case is notable in showing multiple metastases in uterine myomas, as seen also by Schmorl.

Case XV—A woman aged 50 with recurrent carcinoma of the breast had had some recent uterine haemorrhage but no growth was found in curettings microscopically. *Necropsy* disclosed metastases in lungs, liver, kidneys, adrenals, bones, thyroid gland, ovaries and uterine myomas. The uterus contained about 14 myomas, the 2 largest of which in the fundus were each 4 centimetres in diameter, 1 intramural and 1 submucous. These 2 contained multiple white areas of metastatic carcinoma. Sections of 8 of the smaller myomas showed a small focus of carcinoma in 1 only. The normal myometrium and the endometrium were clear of growth.

(13) Hormonal factors influencing the growth of mammary carcinoma

Two seemingly opposed observations on the hormonal control of breast cancer have been made. On the one hand, during the last fifty years there have appeared repeated claims that removal of the ovaries or suppression of ovarian function by X-ray irradiation retards the growth of some carcinomas (Beatson, Lett, Taylor). On the other hand, there are recent claims that the administration of oestrogens is beneficial in some cases of the disease (see for example Haddow *et al.*). Final judgement of the validity of both these claims must be deferred. Whatever beneficial effect loss of ovarian function may have, it must certainly be only relative or temporary, since many carcinomas of the breast develop and grow actively long after the menopause. As regards the possible benefits of oestrogen therapy, many of the favourable claims have been based on single or few cases and the periods of observation have been brief. Further study of large

I have seen in these cases nothing peculiar nothing which might not be written in the ordinary history of cancer of the breast I believe that a nearly similar sequence of events may be observed in other parts. I have seen a persistent 'rawness' of the glans penis, like a long enduring balanitis, followed after more than a year's duration by cancer of the substance of the glans." Paget explained the mammary cancer as a *result* of the surface lesion. "it may be suggested that a superficial disease induces in the structures beneath it, in the course of many months, such degeneracy as makes them apt to become the seats of cancer."



FIG 81 —Case XVII Intra ductal carcinoma of male breast ($\times 120$)

(2) Diverse views on histogenesis

While Paget believed the disease of the nipple to precede the development of cancer in the breast, many later workers took the opposite view that the surface lesion was secondary to an already established intra mammary growth. It is unnecessary to review this controversy in detail. Histological studies have now made it clear that, in those frequent cases in which Paget's disease coexists with a deep seated invasive mammary carcinoma, the former is *not* due to invasion of the nipple from the latter. In many cases there is no anatomical connexion between the two lesions (e.g. Case XX below) and, in some cases of Paget's disease (e.g. Cheatele and Cutler's Case 6 and my Cases XVIII and XIX below), there is no associated invasive mammary growth. Paget's disease is thus primary in the nipple region itself and the frequently coexisting carcinoma of the breast is an independent primary growth.

Microscopical examination shows that in almost all cases of Paget's disease the epithelium of one or more main ducts within the nipple has undergone carcinomatous change (Figs 91-92). Often this growth is still confined to the ducts and has not produced any mass of tumour obvious to the naked eye. In most

nipple contained tortuous dilated ducts with brownish contents and formed an ill-defined mass 2 centimetres in diameter, and microscopical examination showed that the epithelium lining the cystic ducts was carcinomatous but still within the duct confines

Case XVII—A man aged 58 had had an enlarging lump in the breast for 2 years local mastectomy was performed. The breast contained an irregularly loculated cavity 4 centimetres in diameter tightly distended by blood stained fluid and a mass of friable growth. Microscopical examination showed this to consist partly of well differentiated finely papillary growth and partly of more solid irregular papillary carcinoma springing from many parts of the cysts and dilated ducts and still confined within them (Figs 79-81)



Figs 79 and 80—*Case XVII* Intra ductal carcinoma of male breast ($\times 120$)

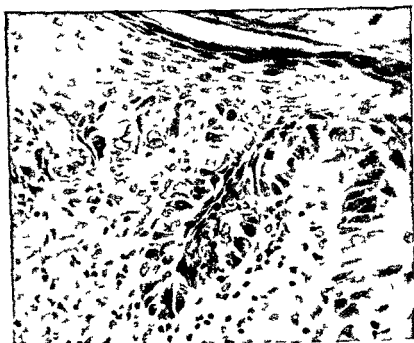
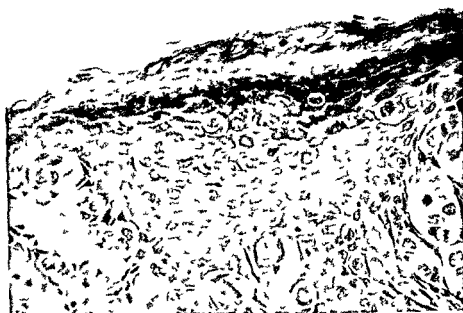
PAGET'S DISEASE OF THE NIPPLE

For excellent descriptions of this disease and discussions of the various views as to its histogenesis see Cheate (1923) Cheate and Cutler Muir (1935 and 1939), and Inglis (1936 and 1946)

(1) Paget's original description

Paget's account in 1874 of the clinical characters of 15 cases of the disease has not been bettered and the following passages from his paper are particularly noteworthy. It has happened that in every case which I have been able to watch cancer of the mammary gland has followed within at the most two years and usually within one year. The formation of cancer has not in any case taken place first in the diseased part of the skin. It has always been in the substance of the mammary gland beneath or not far from the diseased skin, and always with a clear interval of apparently healthy tissue. In the cancers themselves,

to changes in the epidermal cells *in situ* and Paget's disease being due to intra epidermal spread of cancer "



FIGS 83 and 84 — Case XVIII Paget's disease Fig 83 shows that some of the Paget cells are cells of the stratum granulosum and contain eleidin granules Fig 84 shows a part where all the cells of the basal layer have undergone Paget change ($\times 300$)

From my own study of 6 cases of Paget's disease and of the records of others, I am satisfied that it is a form of epidermal carcinoma *in situ*. I agree with Arnd and with Cheate and Cutler that transitions between epidermal and Paget cells

cases the neoplastic change in the ducts extends right up to their exits on the nipple, so that the cancerous duct epithelium and the epidermis affected by the Paget's disease are in continuity. On the other hand in cases in which an invasive carcinoma is present deep in the breast this growth may or may not be in continuity with the carcinomatous duct epithelium in the nipple.

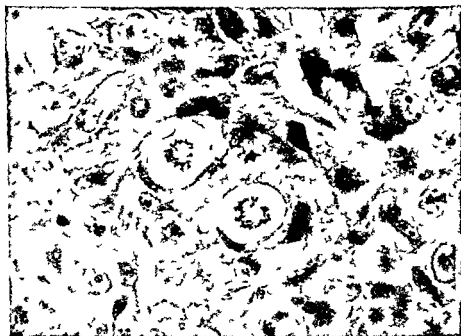
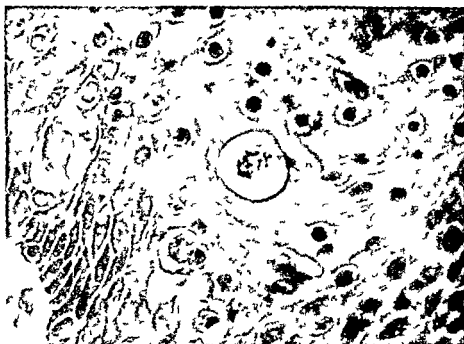


FIG. 82.—Case XVIII. Paget's disease. a general view ($\times 96$)

But there are still two conflicting views regarding the histogenesis of Paget's disease—(a) that it arises as a primary carcinoma of the epithelium of the main ducts in the nipple and that the surface lesion results from intra epidermal spread of the carcinoma cells (Muir, Inglis) and (b) that it is a primary epidermal change—carcinomatous or pre-carcinomatous—and that the neoplastic change in the duct epithelium is concomitant (Cheattle and Cutler). My own studies convince me that the second view is the correct one.

The problem of histogenesis centres around the identity of the 'Paget' cells which were discovered in 1889 by Darier, who at first believed them to be parasitic 'psorosperms'. These are large pale rounded or polyhedral cells present, singly or in small or large clumps in the affected epidermis and often containing mitotic figures. These cells are present in all true cases of Paget's disease (Figs 82-92). Are they invaders from the neighbouring neoplastic duct epithelium or are they cancerous or pre-cancerous cells of the epidermis itself? Arnd showed by Best's method that the Paget cells were rich in glycogen and that transitions between normal epidermal and the glycogen-rich cells could be demonstrated and he accordingly likened Paget's disease to Bowen's "pre-cancerous dermatosis". So also Cheattle and Cutler concluded that 'Paget's cells can be traced developing from epidermic cells in all stages of formation' an opinion endorsed also by Ludford from a close cytological study of some of their material. Inglis on the contrary, could discover no transitions between epidermal cells and Paget cells and therefore concluded that Bowen's and other pre-cancerous dermatoses and Paget's disease are "fundamentally different Bowen's disease being due

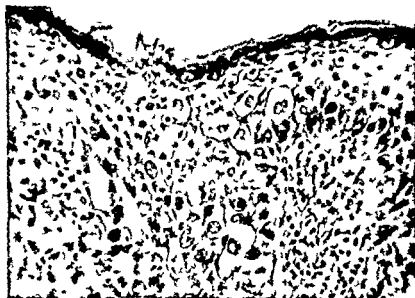
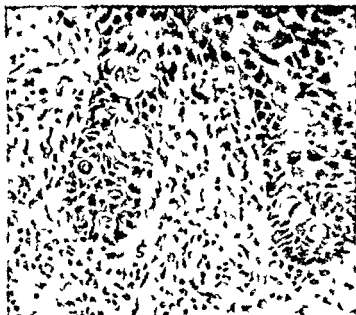
of the special situation of the disease The almost regularly coexisting neoplastic change in the ducts does not prove a duct origin for the Paget's disease, con-



FIGS 87 and 88 —Case XIX Paget's disease showing Paget cells in mitosis ($\times 500$)

comitant change in a field of tissue including both ducts and epidermis is an equally (I think, more) plausible explanation And finally there occur cases like Cheate and Cutler's Case 6 in which Paget's disease is *not* accompanied by neoplasia in the upper reaches of the ducts

are to be seen. Occasionally, indeed, cells which are unmistakably epidermal—e.g. cells situated in the granular layer and containing keratohyalin granules or



FIGS 85 and 86—Case VII. Paget's disease. Fig. 85 shows the characteristic cells, some in mitosis. Fig. 86 shows cells of the stratum granulosum with early Paget changes. ($\times 300$)

swollen spinous cells—are also Paget cells (Figs 83 and 86). Microscopical differences between Paget's disease and Bowen's disease do not warrant the conclusion that they are 'fundamentally different', the cytological peculiarities of Paget's disease, especially the plentiful Paget cells, may be expressions only

had not produced any tumour obvious to the naked eye. Deeper parts of the breast contained no growth. The enlarged axillary glands showed irritative hyperplasia only.



FIGS 91 and 92—Case XVI. Paget's disease. Two views of the intra ductal carcinoma in the nipple region ($\times 120$).

Case XIX—A woman aged 60 had noticed "inflammation" of the nipple and areola and flattening of the nipple for 2 years. Examination showed a circular area of Paget's disease 3 centimetres in diameter but no palpable tumour in the breast. mastectomy

(3) Personally studied examples of Paget's disease

Of my 6 cases, the following exemplify many of the characters of the disease

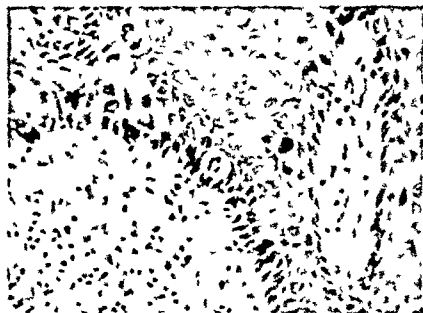


FIG. 10. M. G. 317. Paget's disease of the nipple. (H. & E. 50 \times)

Case 317. A woman, aged 45, with a history of a lump in the right breast, which had been present for some time. The lump was found to be a carcinoma of the breast, and the patient was treated with mastectomy. The histological examination of the tissue showed Paget's disease of the nipple, characterized by the presence of large, dark, irregular clusters of cells. The disease was found to be extensive, involving the entire nipple and areola. The patient died of the disease.

- CHEATLE, G L (1920) Cysts, and primary cancer in cysts of the breast *Brit J Surg* 8 149
- CHEATLE, G L (1920) Benign and malignant changes in duct epithelium of the breast *Brit J Surg* 8 285
- CHEATLE, G L (1923) Paget's disease of the nipple, *Brit J Surg* 11 295
- CHEATLE, G L (1925) Chronic mastitis as a term its fallacy and the danger of its clinical signs *Brit Med J* 1 5
- CHEATLE G L, and CUTLER, M (1931) *Tumours of the Breast* London
(Cheatle's studies of mammary pathology especially of carcinoma are indispensable classics)
- Curtis M R *et al* *Reference* Chapter 6
- DAWSON, E K (1932) Sweat gland carcinoma of the breast *Edinb Med J* 39 409
- DAWSON, E K (1933) Carcinoma in the mammary lobule and its origin *Edinb Med J*, 40 57
- DAWSON, E K (1934 and 1935) 'A histological study of the normal mamma in relation to tumour growth' *Edinb Med J* 1934 41 653 and 1935 42 569 and 633
- DAWSON, E K (1943) Mammary cancer and the menopause *Edinb Med J* 50 721
- DAWSON, E K, and SHAW, J J M (1937) Mammary cancer with generalized telangiectatic carcinoma *Brit J Surg* 25 100
(Mrs Dawson's studies are a valuable well illustrated series)
- Emge L A (1938) *Arch Path* 26 429
- Feldman W H (1932) *Neoplasms of Domesticated Animals* Philadelphia
- Foot N C and Moore S W (1938) *Amer J Cancer* 34 226
- Geschickter C F and Lewis D (1938) *Brit Med J* 1 499
- GILBERT, J B (1933) Carcinoma of the male breast, *Surg Gyn Obst* 57 451 (A useful outline and review)
- Goldsmith W N (1929) *Brit J Derm Syph* 41 270
- HAAGENSEN, C D, and STOUT, A P (1942 and 1943) Carcinoma of the breast' *Ann Surg* 1942 116 801 and 1943 118 1 (Good analyses of the factors influencing operability and prognosis)
- Haddow A *et al* *Reference* Chapter 8
- Handley W S (1922) *Cancer of the Breast and its Treatment* London
- Handley W S (1938) *Brit Med J* 11 113
- Herodotus* Book III Chapters 133 and 134
- Hoffman F L *Reference* Chapter 5
- HUNTER J (1837) *Lectures on the Principles of Surgery* Vol I Edited by J F Palmer
- INGLIS, K (1936) *Paget's Disease of the Nipple and Its Relation to Surface Cancers and Pre Cancerous States in General* London (A valuable review and an excellent atlas of photomicrographs)
- Inglis K (1946) *Amer J Path* 22 1
- Jentzer A (1930) *Schweiz med Wschr* 60 1050
- Kaufmann E (1929) *Pathology* p 1225 (translation by Reimann) Philadelphia
- KEYNES G (1923) Chronic mastitis, *Brit J Surg* 11 89 (A valuable and beautifully illustrated account)
- Khanolkar V R *Reference* Chapter 5 and personal communication
- LANE CLAYPON, J E (1924 1926 and 1928) *Ministry of Health Reports on Public Health and Medical Subjects* Nos 28 32 and 51 (Comprehensive statistical analyses regarding causation treatment and prognosis of breast cancer cf Wainwright)
- LEE B J, and PACK, G T (1931) Giant intracanalicular fibro adeno myxoma of the breast *Amer J Cancer* 15 2583 (A valuable review)
- Leitch A (1909) *Lancet* 11 861
- Lett H (1905) *Lancet* 1 227
- Mackenzie K (1935) *Brit J Surg* 23 234
- MUIR R (1935) The pathogenesis of Paget's disease of the nipple and associated lesions', *Brit J Surg* 22 728
- MUIR, R (1939) Further observations on Paget's disease of the nipple *J Path Bact*, 49 299
- MUIR R (1941) The evolution of carcinoma of the mamma *J Path Bact* 42 155
(Important studies of Paget's disease and of the mode of origin of mammary carcinoma)

was performed *Microscopy*—Typical Paget changes in the epidermis (Figs 85-88) accompanied by intra duct carcinoma in the nipple area but no invasive growth in the breast

Case XX—A woman aged 41 had noticed a discharge from the nipple for 12 months and a mass in the breast for 2 months. Radical mastectomy was performed. The epidermis of the nipple and areola was red and scaly and showed the typical microscopical changes of Paget's disease. The ducts in and immediately beneath the nipple were dilated and showed intra-duct carcinoma without any invasion of surrounding tissues and without any tumefaction visible to the naked eye. One part of the periphery of the breast contained an area of invasive carcinoma 2 centimetres in diameter accompanied by intra duct carcinoma in some dilated ducts adjacent to it. The tissues intervening between this area of growth and the diseased nipple appeared clear of tumour for a distance of at least 3.5 centimetres and this was verified in several micro sections. Other parts of the breast showed some general fibrosis and dilatation of ducts but without tumour. The axillary lymph glands were clear of growth.

Case XXI—A woman aged 39 had had 'eczema' of the right nipple for 18 months commencing 4 months before the birth of a child and extending slowly during 9 months lactation and after. Examination showed a circular red area 4 centimetres in diameter with the retracted nipple at its centre, a large irregular mass in the breast deep to the nipple extending both medially and laterally especially into the axillary tail and a firm mass in the axilla. The amputated breast contained an irregularly pyramidal mass of growth with its apex at the nipple. Microscopically the epidermis showed typical Paget's disease (Figs 89 and 90). The breast showed widespread intra-duct and invasive carcinoma supervening on cystic hyperplasia. The invasive growth was situated mainly in the peripheral parts of the mass while in the nipple region the growth was still mainly within the ducts (Figs 91 and 92).

Cases XVIII and XIX exemplify Paget's disease accompanied by intra duct carcinoma in the nipple but no invasive growth in the breast. Case XX, Paget's disease with intra duct carcinoma in the nipple and a separate focus of invasive carcinoma in the breast, and Case XXI, Paget's disease, intra duct carcinoma and invasive carcinoma all continuous.

REFERENCES

- Arnd W (1926) *Virchows Arch* 261 700
 Askanazy M (1912) *Berlin klin Wschr* 49 2161
 Banks W M (1900) *Lancet* i 684 843 and 990
 Beatson G T (1896) *Lancet* ii 104 and 162.
 BOGEN E (1935) The cause of breast cancer. *Amer J Publ Health* 25 245 (A valuable statistical study.)
 Bonser G M (1935) *J Path Bact* 41 33
 Bonser G M (1936) *J Path Bact* 42 169
 BONSER G M (1945) A microscopical study of the evolution of mouse mammary cancer the effect of the milk factor and a comparison with the human disease. *J Path Bact* 57 413
 Budd J W and Breslin F J (1937) *Amer J Cancer* 31 207
 Bundschuh E (1914) *Beitr path Anat* 57 65
 Burrows, H (1935) *Brit J Surg* 23 191
 Burrows H (1936) *Lancet* ii 1328
 Cappell D F (1931) *Glasgow Med J* 115 181
 Carnett J B and Howell J C (1930) *Ann Surg* 41 811
 Castiglioni A (1941) *A History of Medicine* (Translation by E. B. Krumbhaar) New York
 CHARTERIS A A (1930) On the changes in the mammary gland preceding carcinoma. *J Path Bact* 33 101

CHAPTER 14

EPITHELIAL TUMOURS OF THE SKIN

SKIN TUMOURS are of special interest for several reasons. They can be observed from their inception, they are often removed in early stages so that their mode of origin is readily studied, and much is known about their causation. The skin was naturally enough, the first tissue in which occupational tumours were recognized, and this recognition led to the experimental production of tumours and to the discovery of chemical carcinogens (Chapter 4). An important fact to remember in statistical studies of skin cancer is that, although its clinical diagnosis is fairly reliable in civilized countries, mortality statistics are of no value for making comparisons of its incidence in different communities or for estimating trends, this is because of the high cure rate with modern methods of treatment.

CAUSATIVE FACTORS AND PRE CANCEROUS LESIONS

For valuable outlines and reviews of this subject, see Hueper, Mackee and Cipollaro, Haagensen, and other references given in Chapter 4.

(1) Age incidence

Because of the diversity of known causative factors and the different periods of life at which they operate, little is to be gained by a close analysis of the age incidence of skin cancer in general. Some tumours, e.g. those in cases of xeroderma pigmentosum, some X-ray and radium cancers due to therapeutic applications early in life, and many of the earlier reported cases of chimney sweep's cancer, have developed in youth, but most tumours due to sunlight, tar, oils, varicose ulcers, osteomyelitis sinuses, or old scars, and most of those of uncertain causation have appeared in middle or old age. Age distribution curves while showing cases of skin cancer scattered through the earlier decades, rise steadily during the fourth decade and show a rather blunt summit not a sharp peak in the fifth, sixth and seventh decades. With many of the later appearing skin tumours of known causation, the interval between application of the responsible agent and appearance of the tumour is a very long one—10, 20, 40 years or longer. Hueper gives references to many examples of long induction period. In some series e.g. Savatard's the average age of appearance of basal cell growths has been less than that of squamous cell growths. In most series however, the reverse has obtained, thus Treves and Pack found the mean ages of patients with squamous cell and basal cell carcinomas to be 58 and 61 respectively and Shrek and Gates found the commonest age of onset of the two types to be 57 and 66 respectively.

(2) Sex incidence

Skin cancers as a whole, and almost all of their distinct occupational varieties, occur more commonly in men than in women. Some occupational tumours (e.g. in cotton spinners, chimney-sweeps, arsenic workers and radiologists) are almost restricted to males. Actinic cancers predominate in males, so also do

- Nath and Grewal *Reference Chapter 5*
- Newcomb W D (1924) *Lancet* 1 1056
- Nicholson G W (1921 and 1924) *Guy's Hosp Rep* 1921 71, 222 and 1924, 74 81
- Owens F M and Adams W E. (1941) *Arch Surg* 43 588
- PACK and Le Fevre *Reference Chapter 5*
- PAGET, J (1874) Disease of the mammary areola preceding cancer of the mammary gland ,
St Bart's Hosp Rep Vol X.
- Paul of Aegira* (translation by F Adams) Sydenham Society 1844
- Quinland and Cuff *Reference Chapter 5*
- Ratcliff, H L. (1940) *Amer J Path* 16 237
- Registrar General's Statistical Review *References Chapter 5*
- Riehl G (1926) *Arch klin Chir* 140 320
- Robinson and Grauer *Reference Chapter 6*
- Saphir O and Parker M L (1940) *Amer J Path* 16 189
- SCARFF, R W and SMITH, C P (1942) Proliferative and other lesions of the male breast
 with notes on 2 cases of proliferative mastitis in stilboestrol workers *Brit J Surg* 29 393
 (A useful succinct outline of the pathology of the male breast)
- Schlottbauer C F (1940) *J Amer Vet Med Assoc* 96 632
- Schlottbauer C F and Thurber W B (1929) *J Amer Vet Med Assoc*, 95 361
- Schmorl (1904) *Verh Dtsch path Ges* 8 80
- Sears J B and Schlesinger M J (1940) *New Eng J Med* 223 760
- Severino* Translation by Wilder in *Lange's Selected Readings in Pathology* (1929)
- Shore B R (1931) *Amer J Cancer* 15 221
- Speed H. (1925) *Ann Surg* 82 45
- Taylor G W and Meltzer A (1938) *Amer J Cancer* 33 33
- Taylor G W (1939) *Surg Gyn Obst* 68 452
- Trinea A J and Willis R A (1936) *Med J Austral* 11 222
- TUDHOPE G R (1939) A complex malignant mammary tumour *J Path Bact.*, 49 499
 (A careful study of a remarkable tumour)
- VILPEAU A (1853) *A Treatise on Diseases of the Breast* (Translation by H Mitchell)
 Sydenham Society 1856
- Victorian mortality figures kindly supplied by the Government Statist 1943
- WAINWRIGHT J M (1927) "Carcinoma of the male breast" *Arch Surg*, 16 836 (A
 good review)
- WAINWRIGHT J M (1931) A comparison of conditions associated with breast cancer in
 Great Britain and America *Amer J Cancer* 15 2610 (Compare with Lane Claypon's
 analyses)
- Warren S (1940) *Surg Gyn Obst* 71 257
- Weber F P (1933) *Proc Roy Soc Med* 26 1549
- White J W (1940) *Amer J Cancer* 40 458
- Wildbolz L. (1931) *Z Krebsforsch* 33 681
- Willis R A (1931 and 1941) *Med J Austral* 1931 1 349 and 1941 11 258
- Willis R A (1931) *Amer J Path* 7 187
- Willis R A (1931) *Austral and N Z J Surg* 1 41
- WILLIS R A (1934) *The Spread of Tumours in the Human Body* London
- Willis R A (1939) *J Path Bact* 48 474
- Wood D A and Darling H H (1943) *Cancer Res* 3 507
- Wright A W., et al *Reference Chapter 6*

xeroderma pigmentosum are really actinic cancers, the skin having an inherited super sensitiveness to light Copeland and Martin give a good account of xeroderma pigmentosum, and Mathews discusses photosensitization in relation to actinic carcinomas The commonest sites of skin cancers in outdoor workers are the face and neck and the dorsa of the hands and forearms Actinic cancers may be of either the squamous-cell or basal cell type, and multiple tumours some of one type and some of the other, are frequent They are commonest in the sixth and seventh decades

(d) *X-ray and radium cancers*

X ray and radium cancers, always of the squamous cell type, may be due to either occupational or therapeutic exposure The occupational tumours, now less frequent than in the early days of radiology, occurred usually in men, in the fourth or fifth decade, most commonly on the hands and forearms, and they were frequently multiple Tumours resulting from therapeutic exposure of course show a less regular age, sex and site incidence Haagensen recorded 5 examples of carcinoma from therapeutic X ray irradiation, and Hueper gives other references I have seen several examples of carcinoma arising in areas where other lesions had previously been treated by radium The most tragic of these was in a youth of 18, who for 18 months suffered from a deeply invasive ulcerated squamous cell carcinoma of the neck which arose in a scar resulting from application of a radium pack to a skin tumour when he was 3 years old

(e) *Carcinoma of scars (Marjolin's ulcer)*

Carcinomatous change has been observed in the scars of burns, of lupus vulgaris, of lupus erythematosus and of wounds Usually the tumours appear many years after the infliction of the injury, sometimes as long as 30 or 40 years, but in elderly people with already keratotic skins, a burn or other injury may be followed promptly by a tumour Treves and Pack therefore properly distinguished between acute burn cancers supervening within a few months of the burns, and cancers of old burn scars in which the average induction period in their cases was 32.5 years Scar cancers are usually of the squamous cell type but basal cell growths also occur Treves and Pack's cases comprised 21 epidermoid and 7 basal cell carcinomas, the latter usually in cases in which the burn had been superficial, sparing hair follicles and sweat glands Haagensen reported three instances of basal cell carcinoma at the sites of small burns In one instance some of the scar cancers following lupus vulgaris or lupus erythematosus, in which irradiation has been blamed, but cancer has appeared also in patients who were not treated by X-rays (Savatard) Burns reported a remarkable instance of fatal scar carcinoma following total avulsion of the scalp 21 years after the injury Carcinomatous change in a scar is often multifocal or widespread and the entire scarred area must be regarded as a potentially cancerous field accordingly (Willis, 1945)

(f) *Carcinomas of varicose ulcers*

These occur about equally in men and women most commonly in the fifth sixth and seventh decades, are always squamous celled, and may be multiple or of widespread origin (see Figs 6 and 7)

those arising in scars in osteomyelitis sinuses and in arsenical dermatitis resulting from therapeutic administration of the poison. Carcinoma arising in varicose ulcers affects men and women about equally. Sub-epidermal growths both those of basal-cell type and those of glandular type are commoner in women than in men.

(3) Recognized factors in causation

(a) *Carcinogenic hydrocarbons*

Carcinogenic hydrocarbons are responsible for pitch tar, creosote oil, paraffin and chimney sweep's cancers. These are almost restricted to males appear most frequently in the sixth decade, and are always of the squamous-cell type. Pitch and tar cancers occur most commonly on the head, neck, forearm, hand and scrotum. Oil cancers (notably mule-spinner's cancer) on the scrotum, forearm and hand, and chimney sweep's cancer (now a rare disease) on the scrotum. Multiple tumours are common. A good example is the patient described by O'Donovan, a mineral oil worker who had had 15 tumours removed and who had others developing on his nose, ear, arms, forearms, groins, thigh and leg. It is probable that the Kangri cancers common on the abdominal wall or thigh in Kashmir natives (Neve, Vaughan) are due, not solely to the chronic burns from the Kangri or charcoal heater, but to carcinogenic agents in the associated soot or tarry products.

(b) *Arsenical cancers*

Arsenical keratoses are prone to become carcinomatous. These lesions develop either in men engaged in occupations exposing them to arsenic or in patients of either sex who have taken arsenic medicinally, usually as Fowler's solution for long periods. The tumours are commonest on the limbs, less common on the face and rare on the trunk, and they are usually multiple and often numerous. Both squamous-cell and basal-cell growths occur, about one third of them are basal-celled. (For further details see Franseen and Taylor.)

(c) *Actinic cancers*

The carcinogenic properties of sunlight and ultra-violet light, now fully proved experimentally, were long suspected by dermatologists who noticed the disproportionate frequency of keratoses and of basal-cell and squamous-cell carcinomas of exposed parts of the skin as compared with covered parts in outdoor as compared with indoor workers, in fair-skinned people as compared with dark-skinned people and in sunny as compared with cloudy countries (Molesworth, Harpensen, Phillips). Cancers of the skin in sailors, fishermen, farmers and gardeners are largely due to ultra-violet radiation and the most susceptible subjects are those with fair freckled skin which sunburns easily. As Molesworth insisted, sunbathing is dangerous for people of this complexion. I too have seen several cases of multiple carcinomas of the skin in unusual situations in inveterate sunbathers (e.g. Case III below). Sunlight probably plays a major part in inducing many senile keratoses and skin tumours of unidentified causation. Doubtless other carcinogenic factors co-operate with sunlight. There is every reason to believe that the multiple skin cancers which arise at an early age in cases of

be considered as a possible factor in the causation of skin tumours. This possibility, first suggested, I believe, by Peacock at a meeting of the Pathological Society of Great Britain at Aberdeen in 1946, appears particularly plausible in cases of multiple sub epidermal basal cell growths of predominantly glandular origin, as in Brooke's disease or "turban tumours" (see below). The sebum and sweat of these patients must be searched for carcinogenic substances. Experimentalists also must trace the cutaneous excretion of carcinogens given by mouth or other routes. As Peacock suggested, the association of degenerated parasites (*Demodex*), obstructing the glandular orifices, with some basal cell skin tumours, may not be purely fortuitous; it may be that the obstruction causes local accumulation of carcinogens which are constantly being discharged in small amounts by the skin glands.



FIG 93 — Adamantinoma like structure in carcinoma of sebaceous cyst Case II ($\times 120$)

(4) Sites of tumours of the skin

Clearly the site of a skin tumour will depend on which of the many and diverse causes just outlined are responsible. The main sites of the various causative groups of tumours have already been given briefly, and more will be said on this subject when discussing the several structural types of growths. Most large series of skin tumours record that 50 per cent or more of the tumours were situated on the face or neck, and since arsenic, X ray irradiation or hydrocarbons can be blamed for relatively few of these, this distribution points to the great importance of sunlight in causation. Facial skin cancers are more often multiple than others. Phillips reported that of 1400 patients with skin cancers in Texas, 226 had multiple tumours, varying from 2 to 23 in number, and except for 18 cases with tumours on the hands, all of the multiple growths were on the face. Of the 226 patients with multiple growths, 109 were farmers, often fair skinned. Carcinoma of the conjunctiva, prevalent in horses and cattle (see below), is rare in man.

(g) *Carcinomas of osteomyelitis sinuses*

Carcinomas of osteomyelitis sinuses well reviewed by Bereston and Ney develop in chronic sinuses of long duration—usually 20 or 30, or even 50, years. They are most common in males between 40 and 60 years old and are always squamous-celled. The tibia is much the commonest bone affected. The tumours arise from the skin surface around the sinuses or from the partially epithelialized tracks and spread deeply into the diseased bone along the sinuses. Eliason and McLaughlin saw a man aged 34, with carcinoma of both legs arising in sinuses following compound fractures of both tibiae at the age of 6.

(h) *Carcinomas of other sinuses*

Occasionally carcinoma develops in other chronic skin sinuses. The following is a probable example.

Case I (Mr C H Hembrow's case)—Early in 1935 a woman aged 23 noticed a sore 'pimple or blind boil' near the middle of the gluteal crease. This discharged some pus but failed to heal and it was incised or curetted 6 times during the ensuing 18 months. In September 1936 the lesion appeared as an inflamed ramifying sinus extending deeply into the subcutaneous tissue. It was regarded as probably of developmental origin and analogous to a pilonidal sinus and the extensive tracks were widely excised. Microscopical examination unexpectedly showed the tracks to be lined by a superficial layer of papillary epidermoid carcinoma (Fig. 8). The area remained healed for several weeks and then broke down again and in spite of radiational treatment by November 1937 massive recurrent growth was present.

(i) *Carcinomas of sebaceous cysts*

These have been estimated to occur in from 3 to 9 per cent of such cysts but in view of the frequency of small cysts for which medical advice is never sought these are certainly over-estimates. Caylor's and Benecke's are good accounts of the subject. Most of the tumours are squamous-celled but some have been basal-celled and in Benecke's case the growth had a cystic glandular structure. The following is an illustrative case.

Case II (Mr R C Brown's case)—A fair-skinned farmer aged 60 with many facial keratoses developed a rounded tumour of the temple which was diagnosed as a sebaceous cyst but which was accompanied by a small patch of warty growth in the overlying epidermis. The tumour excised along with an ellipse of skin proved to be a thick walled cyst containing a small amount of sebum. Microscopically the walls showed active squamous-cell carcinoma which had commenced to invade the overlying epidermis and which showed adamantinoma-like structure in places (Fig. 93).

(j) *Carcinoma following special skin diseases*

This has been seen occasionally in association with lupus vulgaris, lupus erythematosus, psoriasis or syphilis (Savatsky, Flint and Gordon Hueper). In cases which had been treated by X-ray irradiation or by arsenic these agents have often been blamed for the supervention of the tumours but in other cases no such treatments had been used. Kraurosis and leucoplakia of the vulva are important pre-cancerous lesions (Chapter 32). Bowen's and other pre-cancerous dermatoses are really forms of intra-epidermal carcinoma (see below).

(k) *Excretion of carcinogenic substances*

Excretion of carcinogenic substances by the sebaceous or sweat glands must

EPITHELIAL TUMOURS OF THE SKIN IN ANIMALS

Many references and illustrations are given in Feldman's book, Chapters 17-19



FIG. 95—Para anal tumour of Kelpie 14 years old—a well-defined ovoid yellowish tumour 6 centimetres in diameter covered by intact skin ($\times 50$)



FIG. 96—Tumour similar to that of Fig. 95 from skin of chest of adult Airedale ($\times 60$)

(1) Dogs

Dogs frequently develop epithelial tumours of the skin. These include epidermal papillomas especially of the ears, adenomas of sebaceous, sweat or

Light is no doubt important also in the causation of tumours of the hands and forearms, where, however, the occupational handling of carcinogenic agents must also operate. While tumours of the face, ears, neck and hands are commoner in men than in women, Shrek found that the reverse applied to tumours of the scalp, trunk and legs.

Taylor *et al* found that the sites of 430 epidermoid carcinomas of the limbs were—hand 284, leg 73, arm 41, feet 32. There was a history of some pre-existing lesion in 193 cases (45 per cent), including senile keratoses in 63, arsenical keratoses in 14, injuries or scars in 36, burn scars in 23, radiation dermatitis in 10, osteomyelitis in 11 and varicose ulceration in 11.



FIG. 94—Cystic adenoma of sweat glands of back of neck of a Pomeranian aged 6. Growth was well defined, lobulated, of sponge-like cystic structure, the cysts containing clear watery fluid ($\times 80$).

Excluding tumours resulting from X-ray or radium burns and from known chemical agents, carcinomas of the fingers are rare. Sigel reviewed 22 recorded cases, and the following two examples deserve mention.

Case III (Mr. C. J. O. Brown's case)—A man of 54, for many years a sun bather on Victorian beaches, developed 2 growths, one on the dorsum of the wrist and the other on the side of a finger. These were excised, and sections showed squamous-cell carcinoma.

Case IV—For years, a man aged 67 had had gout with large tophi, and for 18 months he had had an infected finger tip. Examination showed a typical carcinoma, and amputation was performed. Microscopical examination confirmed the presence of an ulcerated squamous-cell carcinoma of the tip of the finger, and of a large gouty tophus surrounding the interphalangeal joint. There were no gouty deposits in the neighbourhood of the tumour.

Epidermal carcinomas of the external genitalia will be described in Chapters 32 and 35.

and are prone to recur following local removal. Excision of the whole third eyelid is the proper treatment. The tumours grow slowly and for long remain superficial, but they eventually invade the eye or orbit. After the conjunctiva the penis, prepuce and vulva are the commonest sites of skin carcinoma, other sites are much less common.

(3) Cattle

Again the most frequent type of integumentary carcinoma is papillary squamous cell carcinoma of the conjunctiva. But squamous cell cancer of the skin is also common, especially in blonde animals. Drabble's study of skin cancer

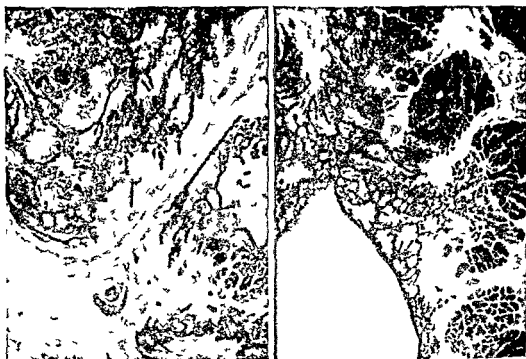


FIG 98—Basal-cell carcinoma of lower lip of adult fox terrier. Tumour which slowly recurred after excision 2 years earlier was 4 centimetres in main diameter and irregularly lobulated with lobules almost discrete from one another. Note the racemose adenoid structure pointing to sweat glandular origin ($\times 50$)

in cattle in Australia showed a striking preponderance of tumours in white or lightly pigmented areas of skin, and pointed strongly to sunlight as an important causative factor. "Brand cancer" is of doubtful significance, its frequency has been falsely exaggerated, and factors other than the brand scar have been overlooked. Carcinoma of the base of the horn is said to be prevalent in India where loads are attached to cattle by the horns (references by Feldman). Squamous-cell carcinoma of the skin of the udder is more common than mammary carcinoma (Drabble).

(4) Sheep, swine and cats

Sheep and pigs only occasionally suffer from cutaneous or conjunctival squamous cell carcinomas, but it must be remembered that these animals are often slaughtered when young. The rarity of skin cancer in cats, however, denotes

ceruminous glands (Fig 94), invasive squamous cell carcinomas of the usual type liable to ulceration and metastasis well circumscribed sub epidermal non metastasizing growths most frequently but not invariably from the peri anal area undoubtedly arising from the glands and consisting of rather characteristic columns and clumps of large polyhedral cells with only a slight tendency to cornify (Figs 95 96), and basal cell tumours of glandular or hair matrix origin, which grow in adenoid or reticular patterns (Figs 97 98). A prevalent idea that dogs have few or no sweat glands is false, sweat and apocrine glands are plentiful in dogs and are the principal source of their common basal celled and adenoid skin tumours. Nothing is yet known of the causation of skin tumours

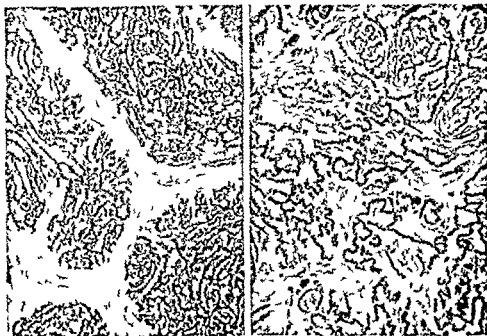


FIG 97—Sub-epidermal basal-cell growth of reticular pattern from neck of a mongrel dog (A) shows lobular structure pointing to sweat glandular origin ($\times 50$ and 85)

in dogs. Their distribution—more often on hairy parts of the trunk and limbs than on bare parts of the face—shows that light is not an important factor and their frequent origin from the glands suggests the possible action of carcinogenic substances excreted in sebum or sweat. The most frequent site of squamous cell carcinomas of the trunk is the skin of or close to the prepuce and these juxta preputial tumours are sometimes multiple. Rudduck and I saw a male Alsatian aged 9 with a squamous cell carcinoma arising in the centre of the squatting callosity over the olecranon there were metastases in the axillary lymph glands.

(2) Horses

Chronic papillary squamous cell carcinoma of the conjunctiva is common, Rudduck and I studied 13 cases (Fig 99). These tumours arise mainly in animals between 5 and 10 years old usually from the third eyelid they are often demonstrably of diffuse origin over a considerable field of tissue are sometimes bilateral,

thickness, ridge pattern, stratification pattern, pigmentation, and depth of papillae, and at certain special regions, such as the muco cutaneous junctions, the eyelids and conjunctiva, the external auditory meatus, the nipples, and the several parts of the external genitalia, the epithelium has locally distinctive characters. In spite of this structural diversity, however, the entire epidermis and its various appendages form a single system of closely allied components, all of which have developed from a common precursor, the foetal epidermis, and all of which in the adult show similar reactions in many pathological conditions including tumours. These tumours, like their parent epithelia, show great structural diversity, yet form a unified group in which, though we properly distinguish several main types, these are connected by growths of intermediate structure and behaviour. No sharp distinction is possible between papilloma and carcinoma, between basal cell and squamous cell growths, between basal-cell carcinoma of the epidermis (rodent carcinoma) and sub epidermal basal cell growths arising from hair follicles or glands or between the latter and tumours of plainly glandular structure—adenomas or adenocarcinomas—of the dermal glands. Attempts to name and classify skin tumours on the assumption that each has arisen from either basal or spinous cells, or from either surface epidermis or hair follicles or sebaceous glands or sweat glands, have created artificial distinctions and a redundant terminology. Growths of similar structure may and do arise from any or all of these sites. Hence, the following tabulation of the main structural variants of epithelial growths of the skin, while necessary and useful, does not imply any biologically sharp separations.

- (1) *Papilloma* (a) Squamous or horny and unpigmented (b) Pigmented
- (2) *Squamous-cell carcinoma*
- (3) *Basal cell carcinoma* (a) Superficial or rodent type
- (b) Sub epidermal type
- (c) Mixed basal and squamous cell carcinoma
- (d) Basal cell carcinoma of the tibia
- (4) *Tumours of glandular structure arising from sebaceous glands*
- (5) *Tumours of glandular structure arising from sweat glands*
- (6) *Tumours of glandular structure arising from other special glands*
- (7) *Intra epidermal carcinoma*

(1) Papillomas of the epidermis

(a) Squamous or horny unpigmented papillomas

The commonest form is the cutaneous horn consisting of a localized sessile overgrowth of the epidermis surmounted by a short or tall conical mass of firmly attached keratin. Less usual are bulky cauliflower papillomas either sessile or pedunculated. Carcinomatous change occasionally supervenes in previously simple papillomas of long duration. Infective papillary overgrowths of the epidermis, such as warts or venereal condylomas, are not true tumours.

(b) Pigmented papillomas

Also called 'seborrhoeic keratoses', 'senile warts', or 'acanthotic naevi', these are common in the skin of middle aged and old people, as slowly growing sessile or pedunculated brown or grey firm masses with a finely nodular or

a real relative insusceptibility to this disease. Rudduck and I saw a basal celled adenoid tumour of the neck of an adult Persian cat

(5) Rodents

The spontaneous and experimentally induced epidermal tumours of mice are too well known to call for description. Rats, rabbits and guinea pigs are less susceptible, but it is of interest to note that actinic cancers are readily induced in rats (*see* Chapter 4), that these may be of either squamous cell or basal cell type and that Bullock and Curtis saw spontaneous basal cell as well as squamous-cell carcinomas in rats



FIG 99.—Papillary carcinoma of third eyelid of horse aged 10 ($\times 60$)

(6) Birds

Birds with skin tumours have seldom been described. Emmel reported examples of epidermoid cancer of the feet of wild birds. Rudduck and I saw a papilloma of the base of a claw in a magpie

(7) Lower vertebrates

The few records of tumours of the skin glands in amphibians, of papillomas in lizards and of carcinomas of the gill region in fish were mentioned in Chapter 6

THE VARIETIES OF EPITHELIAL TUMOURS OF THE SKIN

The integumentary epithelium shows great diversity of structure—it includes the surface epidermis, hairs and hair follicles, nails, sebaceous, sweat and apocrine glands. The epidermis itself varies markedly in different parts of the body, in

growths shows that the fields of origin of these are commonly areas of skin of not less than 1 or 2 centimetres diameter. The epidermis marginal to a young tumour often shows gradual hyperplastic thickening as it nears the tumour, and the hyperplastic epithelium is gently continuous with the neoplastic without any abrupt demarcation. The epithelium of the young tumour is often highly differentiated and epidermis like, and its cancerous nature is revealed only by the invasion of the dermis. These features are exemplified in Figs 2 to 5. Carcinomas arising in scars, ulcers or other extensive pre-existing lesions are often demonstrably widespread or multicentric in origin, the epithelium in the whole field of the pre-cancerous lesion may become cancerous simultaneously or successively (Figs 6 and 7).

(b) *Microscopical structure*

The familiar structure of well-differentiated cornifying squamous cell or epidermoid carcinoma is described and depicted in every text book, and is sufficiently illustrated in Figs 2 to 7. Epidermal carcinomas show gradations between nearly epidermis-like structure and diffuse anaplastic growth not recognizably epithelial. The following special structural features deserve comment.

(i) *Spinous cells*—Spinous cells with plain intercellular bridges are often plentiful in well-differentiated growths with cornified "cell nests" or "epithelial pearls", and are sometimes present in tumours in which cornification is not conspicuous.

(ii) *Spindle-shaped cells*—These are prominent in some tumours. Usually they are components of well-defined epithelial masses but occasionally they occur in diffuse areas of growth and mimic "spindle cell sarcoma" in appearance (For a good account of spindle cell carcinomas of the skin, see Martin and Stewart).

(iii) *"Tubular acanthoma"*—This is a name sometimes applied to areas of epidermoid carcinoma consisting of narrow ramifying epithelial strands traversing invaded tissues. The name is inappropriate since the strands are solid and do not contain a lumen. Tumours showing this structure are highly malignant, their margins are often ill-defined because of the wide zone of microscopic infiltration, and they frequently metastasize.

(iv) *Pseudo-glandular structures*—Pseudo-glandular structures may be produced by either disintegration of the keratinized centres of epithelial masses (as in Fig 19) or by accumulation of glycogen in the tumour cells. The latter change produces a soft juicy tumour in which pseudo-glandular spaces and cysts containing watery fluid rich in glycogen readily develop, and the microscopic appearance of such tumours closely resembles that of clear-celled carcinoma of the kidney. On p. 435 of my 1934 work, under the diagnosis of "richly glycogen-containing cystic papillary adenocarcinoma of the skin", I described a bulky fungating tumour of the neck in a woman aged 72, which I now recognize to have been really an epidermoid growth with great accumulation of glycogen (Fig 20). Metastases in the lungs and liver were also rich in glycogen and of similar clear-celled and cystic structure.

(v) *'Adamantinoma'-like structure*—This is sometimes seen in ordinary squamous cell carcinoma (Fig 93) as well as in the basal cell tumours of the tibia (see below).

corrugated surface. They occur on the face, trunk or limbs. They may be solitary or multiple, multiple ones often occurring as a group in a particular region. I have seen a crop of eight of them restricted to the skin of the vulva. Fox has given a good description of these growths and has rightly deprecated the habit of calling them naevi.

Microscopically (Fig 100) these growths consist of folded thick layers of epithelium clothing slender dermal papillae. The epithelium consists mainly of small cells of basal or baso spinous type with ill defined prickles. The cells contain



FIG 100—Pigmented papilloma of groin from a man aged 62 ($\times 120$)

varying amounts of finely granular brownish pigment. The epithelium also encloses small horny foci or pearls which however are continuous with the horny stratum corneum on the surface of the papilloma. J W Dawson aptly said of the microscopical structure of these tumours. The appearances in many cases are difficult to describe so striking is the appearance of the horny pearls and the islets of mesoblastic tissue among the sheets of cells but it is almost as if a thick disc of small epithelial pigmented cells rested on the corium and mesoblastic cores had canalized it in various directions raising the epithelium into papillae covered with stratum corneum. These growths have nothing in common with pigmented moles: no naevus cells are present and when a malignant growth develops in one of them, a rare event, this growth is a squamous cell carcinoma.

(2) Squamous-cell carcinoma of the skin (epidermoid carcinoma, acanthoma, epithelioma)

(a) Mode of origin

Elsewhere (1944 and 1945, and Chapter 7) I have given the evidence that squamous-cell growths of the skin arise not from single minute foci but from fields of prepared epidermis of small or great extent. Study of solitary localized

previously reported cases of calcifying "epithelioma". Of more recent accounts that of Côté is excellent. The name "epithelioma" is misleading; these growths have little in common with epidermoid carcinomas, and it is questionable whether they are really tumours at all. They may be only sebaceous or epidermal cysts with initial irritational overgrowth of the epithelium followed later by degeneration.

(3) Basal-cell carcinoma

This type of growth may arise in the epidermis itself, producing first a plaque like thickening of the skin and later a slowly enlarging ulcer—"Jacob's ulcer"



FIG 101—Rodent carcinoma of back showing relationship to degenerating hair shafts ($\times 80$)

(Jacob, 1827) or 'rodent ulcer'. Or it may arise, not from the epidermis, but from pilo sebaceous follicles or sweat glands deep in the dermis, producing a non ulcerating well defined rounded or lobulated sub epidermal or subcutaneous growth, variously designated Brooke's tumour', "cystic adenoid epithelioma", 'sub-epidermal benign basal cell tumour', 'turban tumour', etc. As Krompecher long ago showed, no sharp separation between basal-cell growths of the superficial and deep types is possible, growths similar in structure and behaviour may arise from basal cells in any part of the epidermis and its appendages. Good accounts of these tumours include those of Krompecher, Lohmer, Molesworth and Haythorn.

(a) Basal cell carcinoma of superficial origin (rodent carcinoma)

(i) *Distribution*—Most of these tumours occur on the face or neck but any part of the skin may be affected—the trunk, limbs (Newland), vulva (Wilson) anus (Lawrence), etc. The specimen depicted in Fig 9 was from the cubital fossa that of Fig 11 from the chest, and that of Fig 101 from the back. On the face the most common sites are on the lower eyelids

(c) *Local spread*

Epidermoid carcinomas of the skin differ widely in their invasiveness. Many of them are of relatively low malignancy, growing and penetrating into the underlying tissues only slowly, and no sharp distinction between papillomas and these chronic carcinomas can be made. Typical of the chronic relatively benign kind of carcinoma are those of the dorsum of the hand in elderly outdoor workers, many of which long remain freely movable on the deep tissues and non-ulcerated. Exacerbations of growth are not unusual, a formerly slowly growing well localized tumour taking on more rapidly invasive growth. Such changes in rate of growth of a tumour are sometimes reflected in its structure, part of it consisting of the older well differentiated growth and part of it of younger more anaplastic and more invasive elements (Fig. 4). Once a tumour has penetrated through the dermis into the subcutaneous and deeper tissues, it often extends more rapidly in these. Tumours arising in scars or chronic ulcers usually remain superficial for long periods, but they often replace the superficial tissues over wide areas, in this extension widespread cancerous change plays a part as great as, or greater than, invasive replacement (Willis, 1945). Once a scar cancer has penetrated through the avascular scar tissue into the deeper tissues, it often spreads more rapidly (Treves and Pack).

Deep to and around early carcinomas dermal changes, especially in the elastic tissue, are prominent. The elastic fibres commonly show great increase in both number and size and degenerative swelling and fusion. The altered elastica is often plainly visible in haematoxylin stained sections as a bluish layer up to 2 or 3 millimetres thick (Willis, 1944).

(d) *Metastasis*

From most kinds of epidermoid cancers of the skin, metastasis occurs relatively late and infrequently. Shrek found that 16 per cent of these tumours metastasized to lymph glands, and that the site of the primary growth did not greatly affect the liability to metastasis. Taylor *et al.* however found considerable differences: lymph nodal metastases from primary growths of the fingers were present in 9 per cent of cases, of the hands 15 per cent, arms 26 per cent, feet 41 per cent, and leg 36 per cent. In my experience squamous cell cancers of the face and neck frequently produce metastases. X-ray cancers, though often slow to metastasize, eventually do so in a considerable proportion of cases—from 25 to 70 per cent in various reported series (Haagensen, Hueper). Osteomyelitis carcinomas rarely metastasize; Bereston and Ney could find only 7 reported instances. Metastases are infrequent also from cancers of scars, chronic ulcers and sebaceous cysts. Most metastatic growths from skin tumours are in the regional lymph glands; blood borne metastases are less frequent (for some examples see my 1934 work, p. 416, Treves and Pack, and Cookson).

(e) *Note on calcified epithelioma of the skin*

There is a group of rare sub-epidermal tumours composed of masses of well differentiated cornifying epithelium which undergoes extensive necrosis and calcification. The tumours arise chiefly in young people, including children, most often in the head, neck or arm; they are well defined, grow slowly, may cease growing and never metastasize. Ossification in the stroma is not unusual; a good example of this was described by Nicholson (1917) who also reviewed

the basal layer of the epidermis, with either rounded or angular outlines, the marginal parts of the downgrowths showing a distinct layer of cubical or columnar cells and their centres consisting of small dark-staining polyhedral, ovoid or



FIG 104—Superficial but non ulcerated cystic basal-cell growth of back of neck of a woman aged 45 ($\times 6$)

fusiform cells devoid of any special arrangement Inter cellular bridges are usually missing or indefinite, but are sometimes clearly present Remarkable



FIG 105—Detail of Fig 104 ($\times 85$)

in view of the slow growth of the tumours is the presence of plentiful mitotic figures in the cells the explanation may be that some unknown factor arrests or retards mitosis in the later stages Minute rounded cysts often develop in

along the side of the nose and across the middle of the cheek Glasunow and McFarland *et al* saw in this distribution a relationship to the embryonic facial clefts and supposed the tumours to be "facial cleft carcinoids" derived from developmentally sequestered cells No real evidence exists to support this purely



FIG. 102.—Satellite focus of origin from basal layer of epidermis at margin of a main growth 3.5 centimetres in diameter ($\times 85$)

speculative suggestion indeed, the distribution of tumours is opposed to it, for many quite typical rodent carcinomas arise on parts of the face and neck remote from the facial clefts or in other parts of the body The predilection of the tumours for the middle third of the face and the nasal margins is probably related to the distribution of sebaceous glands and perhaps to the incidence of light

The studies of Lohmer Molesworth Willis (1945) and others, of early superficial basal-cell growths show unmistakably that these often arise not from single minute foci but from multiple foci in considerable areas of epidermis, and that the basal-cells of hair follicles and shafts and of the skin glands may



FIG. 103.—Superficial but non-ulcerated cystic basal-cell growth of back of an elderly man who had 11 separate similar tumours on various parts of body ($\times 15$)

also participate in the cancerous change (Fig. 101) Clinically multiple tumours on the face or elsewhere are common very numerous tumours on many parts of the body may occur (e.g. Case XIV of my 1945 paper) and microscopical study of the excised specimens will often disclose minute separate foci of growth in the epidermis marginal to the clinically obvious tumour (Figs. 11 and 102) Haythorn particularly stressed the pilo sebaceous origin of basal cell carcinomas and advocated the title "hair matrix carcinoma"

(ii) *Microscopical structure*—This is depicted in the figures The following features may be noted Many tumours show multiple solid downgrowths from

but they can neither be subdivided into distinct groups, either clinically or histogenetically, nor separated sharply from the superficial basal cell growths of rodent type on the one hand or the truly glandular skin tumours on the other. Any subdivision is arbitrary and leaves borderline cases between the sub groups. The multiplicity of names and views advanced regarding non ulcerating cystic basal cell growths of the skin is well set forth by Warvi and Gates, and valuable accounts include those of Krompecher, Savatard (1922 and 1938) and Ronchese.

(1) *Distribution*—Sub epidermal basal cell growths show less predilection for the face and neck than their epidermal counterparts, many of them arise on

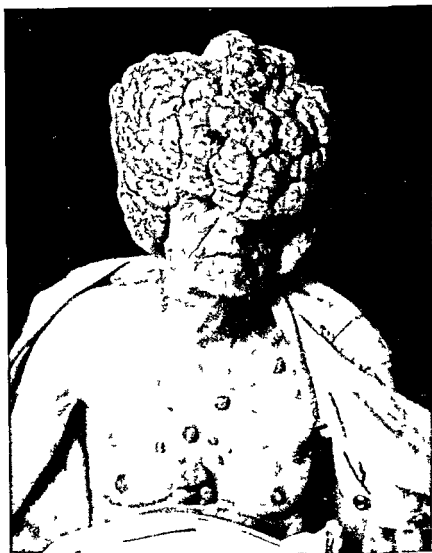


FIG 107 — Turban tumours in an old woman slowly enlarging since early adult life

the trunk, limbs and scalp. A remarkable group of cases exists in which very numerous tumours develop in the skin of the thorax, neck, face and scalp, usually appearing first during adolescence and increasing slowly in size and number. Goldsmith and Freudenthal saw a boy of 7 in whom multiple basal-cell growths of the face and neck had first appeared at the age of 5. In Paul and Inglis's case multiple facial tumours were noticed at the age of 2. The disease is often familial, and is commoner in females than males. Brooke and Fordyce described cases

the epithelial masses (Fig 103) and these may become so numerous as to produce conspicuous honeycomb patterns (Figs 104 105) Parts of the tumours may thus acquire a spurious glandular appearance The epithelium often displays also branching reticular and folded patterns (Fig 106) All of these variations of structure may be seen in one tumour Metaplastic goblet cell formation occurs occasionally (Nicholson 1923 and Šikl)

(iii) *Local spread*—The name 'rodent' is appropriate The tumours are slowly invasive and destructive Untreated growths on the face may eventually destroy most of the facial soft tissues and bones or may penetrate to the skull or brain Thanks to prompt radiational and surgical treatment, the frightful destructive power of these eroding tumours is now rarely seen Elsewhere (1930) I have reported penetration of the apex of the lung and of the spinal canal by a



FIG 106—Reticular structure of basal-cell carcinoma ($\times 85$)

rodent cancer of the neck There occurs also a type of superficially spreading basal cell carcinoma which does not ulcerate deeply and which tends to heal in parts this is Molesworth's superficial cicatrizing type and Brown and McDowell's field fire carcinoma

(iv) *Metastasis*—Metastasis of basal cell carcinoma to the regional lymph glands has rarely been seen (Beadles Finnerud Mulzer) The only acceptable report of metastasis by the blood stream is that of De Navasquez who saw deposits in the lungs and bones from a structurally typical basal-cell tumour of the forehead Niles's case of supposed 'basal cell epithelioma' with metastases is unacceptable the figures show an active squamous-cell growth

(b) *Basal cell growths of sub epidermal origin*

Sub epidermal basal cell growths arising from the pilo sebaceous epithelium and the sweat glands are of very variable structure distribution and behaviour ,

clearly contributing nothing to it, but in other cases basal cell downgrowths from the epidermis co exist with the sub epidermal masses of tumour, as in Fig 9 The shape and structure of some "rodent ulcers" suggest the supervention of surface ulceration in a predominantly sub epidermal tumour

(.ii) *Growth*—Growth of the sub-epidermal basal cell tumours is slow and expansive in type They do not infiltrate surrounding tissues, and ulceration takes place only accidentally, or because the tumour includes superficial growth

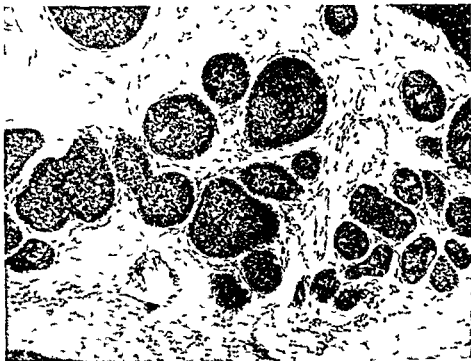


FIG 109—Detail of Fig 108 showing that the small tumour clumps are sweat glands filled and distended by solid basal-cell growth ($\times 90$)

of "rodent" type Metastases never develop These characters explain the "benign" reputation of the group Streitmann's interpretation of a quiescent lymph nodal metastasis of 15 years duration in his case of Spiegler tumours is dubious, no lymphoid tissue was found around the supposed metastatic growth, which may have been one of the multiple primary tumours unusually situated in the supraclavicular region

(c) *Mixed basal cell and squamous cell carcinoma*

While most carcinomas of the skin are readily classifiable as of either squamous-cell or basal cell type tumours of intermediate structure and behaviour occur (Krompecher, MacCormac, Darier, Montgomery, Brown and McDowell) Some tumours show separate areas of the two types of growth, others show throughout an intermediate or combined structure, i.e. the general structure of basal cell carcinoma but with scattered cell nests or areas of distinct spinous cells (Fig 114) Such tumours maintain their intermediate structure in their lymph nodal or blood borne metastases (Willis, 1930) Patients with multiple tumours, some squamous celled and others basal celled, may also have tumours of intermediate or mixed type (Brown and McDowell) Mixed tumours may develop in cases of xeroderma pigmentosum (Geschickter and Koehler)

in which the tumours were distributed mainly on the face and chest and this syndrome is often designated Brooke's or Fordyce's disease. Brooke's name 'epithelioma adenoides cysticum' is frequently used for growths of this type. When the tumours predominate on the scalp as in the case depicted in Fig. 107 they are 'Spiegler's tumours' or "turban tumours" (Ronchese). The following case is noteworthy.

Case V (Mr. A. F. MacLure's case)—An unmarried woman first came under observation at the age of 40 with numerous rounded sub-epidermal growths measuring up to 2 centimetres in diameter scattered over the scalp, face, neck and upper part of the thorax. These had first been noticed at the age of 20 and had slowly increased in size and number. An interesting feature was that none had developed in the area of a childhood burn scar on the neck. No family history of skin tumours was given. A tumour excised from the skin of the chest showed the typical structure of a cystic basal-cell growth clearly related to sweat glands.

Cases with solitary or few non-familial tumours of similar type are quite common; the tumours usually not appearing, however, until middle age (see Figs. 108, 109).

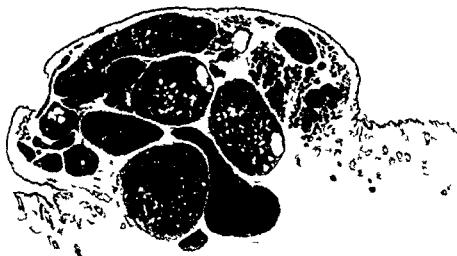


FIG. 108—Solitary sub-epidermal mainly solid basal-cell growth from scalp of woman aged 45 ($\times 7$).

(i) *Structure*—(Figs. 9, 10, 108, 113). The tumours consist of well-defined masses of closely packed dark-staining epithelial cells generally resembling those of rodent carcinomas. In young tumours the appearance of smaller masses often points to their origin in one or more groups of sweat glands (see Figs. 9, 10, 108 and 109 and Ronchese's Figs. 7 and 8) in their shape and distribution the epithelial clumps resemble sweat glands or ducts filled and distended by tumour cells *in situ* and the presence of thick hyaline basement membranes around them often enhances the resemblance to sweat glands. Evidence of the participation of sebaceous glands and hair follicles may be present also, but is less frequent. The larger masses of epithelium show cystic changes, pseudo-glandular structures, and sometimes the reticular and laciform patterns more commonly seen in rodent carcinomas. The surface epidermis is often intact and unaltered over the tumour,

The occurrence of tumours of intermediate type serves to remind us that the basal cells and spinous cells of the normal epidermis are not sharply distinct and that the former also possess intercellular bridges. Pathologists, by their nomenclature, have over emphasized the distinctions between basal cell and spinous cell growths—the truth is that these are only variants of one histogenetic group of tumours, and it is a matter for surprise that tumours of mixed structure are not more frequent than they are.

(d) *Basal cell carcinoma ("adamantinoma") of the tibia*

Less than a score of examples of this rare tumour have been reported, including those of Fischer, Baker and Hawksley, Richter, Ryrie, Holden and Gray, Rehbock and Barber, Wolfort and Sloane, Oberling *et al.*, Thomas, and Petrov and Glasunow. The lesion is a distinctive one. A slowly-growing tumour develops in the middle or lower third of the shaft of the tibia, skiagrams of which show a well defined area of bone destruction, sometimes occupying the centre of the bone, sometimes appearing as an eccentric defect usually of the anterior part of the shaft. Dissection reveals that even in cases in which the radiographic appearances showed a prominent central lesion, the tumour also involves the surface. However, from many of the cases reported, it is clear that the tumours originated in the periosteum or bone and not in the overlying skin or soft tissues, for these were unaffected. Most of the patients have been middle aged males, but Richter's patient was a 12 year old Javan boy, and Thomas's patient was a girl aged 19 who had had a lump in her shin since the age of 12. In most cases there has been a definite history of previous injury to the area but not a severe or penetrating injury. Petrov and Glasunow refer to a similar tumour in the ulna of a woman aged 22 described by Maier.

(i) *Microscopical examination*—Microscopical examination shows an epithelial growth usually of distinctly basal cell type, but sometimes, as in Rehbock and Barber's case, with cell nests or other epidermoid characters. A loosely reticular arrangement of the cells in the centres of the epithelial masses in some of the tumours has resembled that seen in "adamantinomas" of the jaws, and it was this feature which led the first describers of these growths (Fischer, Baker and Hawksley and Ryrie) to call them "adamantinomas" of the tibia. The propriety of this name, however, is more than questionable—not only is there no warrant (save an occasional structural resemblance) for regarding the tibial and the oral tumours as related but the name 'adamantinoma' is inappropriate even for the oral tumours themselves (see Chapter 16).

(i) *Histogenesis*—Two views must be considered (a) that the tumours arise from developmentally misplaced islands of epidermal cells in the periosteum or bone (Baker and Hawksley, Petrov and Glasunow) or (b) that they arise from cells of the epidermis or its appendages displaced into the periosteum by trauma (Ryrie). Those favouring the first view point to the difficulty of imagining how non-penetrating injuries could dislocate adult epidermal cells into the periosteum while those advocating the second view point to the usual history of definite injury in the cases and to the superficial position of the tibia immediately beneath the skin. Ryrie thought it quite possible that shearing injuries in this region might detach deep hair-follicles from the epidermis and that during repair such fragments might become incorporated in the bruised periosteum. This

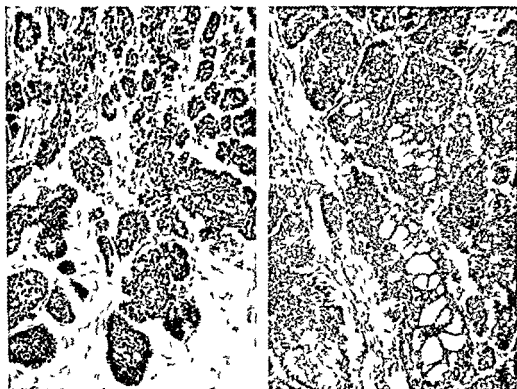


FIG. 110—Solid and cystic basal-cell growth from solitary sub epidermal tumour of neck of a man aged 59 ($\times 80$)

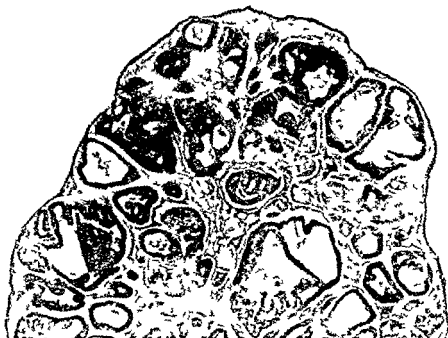


FIG. 111—Part of a pedunculated sub-epidermal cystic basal-cell growth of areola of nipple of a man aged 50 ($\times 6$)

sweat-gland tumours, a tumour predominantly of solid or cystic basal cell type may contain areas of acinar structure (Figs 112, 113), and vice versa. Further, attempts to subdivide sweat glandular tumours into 'syringomas' supposed to have arisen from the ducts, and "spiradenomas" or "hydradenomas" supposed to have arisen from the secreting acini, or to segregate cystic members of the group under such captions as "syringocystadenoma", are unjustified and unnecessary. The adenomas and adenocarcinomas of sweat glands and ducts form a single group, the variants of which do not call for special names. There is no need either to separate sweat glandular and apocrine tumours. (For a useful description and review with many references, see Gates, Warren and Warvi.)



FIG 113—Detail of Fig 112 showing sweat glands continuous with or differentiating from solid basal-cell growth ($\times 170$)

The tumours may be solitary or multiple, and may affect any part of the skin especially the scalp, face, chest, axillae, vulva and buttocks. They are not unusual on the hands or feet. They may appear at any age but are most frequent in the middle aged or elderly, women are affected more often than men. In one group of cases, multiple tumours of the trunk have appeared about puberty, usually in girls, and it has been suggested that these are related to some developmental anomaly of the glands.

(i) *Structure*—(Figs 94, 115) The tumours usually form well defined but not encapsulated growths in the dermis or subcutaneous tissues. They may show a well developed acinar structure resembling that of sweat or apocrine glands, or they may be predominantly cystic, papilliferous or solid. The stroma is variable in amount, it may be abundant, and may show peculiar hyaline or mucoid changes. Smard described an unusual tumour of the palm which had a pleomorphic structure recalling that of a salivary tumour, including not

suggestion¹ I think plausible careful microscopic study of the tissues of scarred adult shins might clarify it Kreibitz saw a shin tumour of pleomorphic structure like that of the salivary tumours unattached to either the skin or bone

(iii) *Growth*—The tumours grow slowly and metastasis to the inguinal lymph glands has been proved in only one case (reference by Petrov and Glasunow) Adequate local excision or amputation is usually curative

(4) Tumours of glandular structure arising from sebaceous glands

Warren and Warvi have reviewed the hyperplasias and tumours of sebaceous glands Hyperplasias such as rhinophyma should be distinguished from tumours,

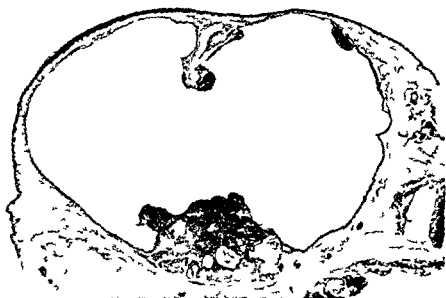


FIG 112—Solitary sub-epidermal cystic basal-cell growth of arm of a man aged 69 ($\times 6$)

so also should the enlargements of sebaceous glands—'sebaceous naevi'—accompanied by other developmental anomalies in Pringle's disease True sebaceous adenomas and adenocarcinomas are rare Most of them occur on the eyelids face or scalp in middle aged or old subjects, either men or women Those of the eyelids arise from the Meibomian glands The tumours grow slowly distending the overlying epidermis, ulceration is usually long delayed, and metastasis to the regional lymph glands infrequent Warren and Warvi point out that only small areas of a carcinoma may show typically sebaceous structure and the tumour may be mistaken for an ordinary squamous cell or basal cell growth Indeed, it is needless to distinguish sharply between sebaceous tumours and basal cell or squamous cell growths arising partly from pilo sebaceous units, these differ not in histogenesis but only in the kind of differentiation they show Innis and Whittick saw an adenocarcinoma of the Meibomian glands in a dog

(5) Tumours of glandular structure arising from sweat glands

Sub epidermal basal cell growths of sweat glandular origin have been described above No sharp distinction can be drawn between these and adenomatous

not be distinguished from basal cell carcinomas", and that several recorded sweat gland tumours "present difficulties of interpretation, because of atypical



FIG 115—Sweat glandular adenoma of finger from a man aged 72 ($\times 100$)



FIG 116—Squamous metaplasia of sweat glands and ducts from multiple small papular lesions of skin of front of chest of a woman aged 22 present since childhood ($\times 120$)

characteristics such as pearl formation'. For reasons already given, I believe that it is impossible to make sharp histogenetic and structural distinctions between

only glandular tissue but also squamoid areas, mucinous secretion and pseudo cartilage. Sumard regarded the growth correctly in my opinion as a tumour of sweat glands in which the cells had acquired mucus secreting functions but it is not necessary to assume with him that there was a metaplasia of epithelial tissue into cartilage. (See Chapter 17) Myo epithelium certainly occurs in some well differentiated sweat gland tumours but the descriptions and figures of some writers e.g. Sheldon, are unconvincing.



FIG 114—From rodent carcinoma of nose showing cornification in predominantly basal-cell growth ($\times 85$)

The following case is notable not only because the tumour showed combined glandular and basal cell structure but also because of its unusual history and situation.

Case VI—In 1938 a girl aged 18 had a subcutaneous tumour 1.5 centimetres in diameter removed from the volar aspect of the distal part of her thumb. This proved to be a synovium of fibrous and giant-celled type. In 1943 a tumour of several months duration was excised from the same situation. This proved unexpectedly to be a carcinoma partly of typical basal-cell structure partly of epidermoid structure and partly of acinar structure clearly derived from sweat glands. Were the 2 tumours quite unrelated and coincidental or is it possible that some carcinogenic stimulus perhaps related to a penetrating injury may have evoked successive neoplasia in 2 distinct tissues? The patient was a seamstress but did not recall having pricked her thumb.

Gates *et al* sharply distinguished sweat gland tumours from basal-cell tumours and held that the origin of basal-cell carcinomas from the sweat glands is unlikely on theoretical grounds and has yet to be proved. Yet they admitted that in some sweat gland tumours the typical appearance is not seen and there may be a close resemblance to basal cells or squamous cells, that in some tumours the structure has a certain resemblance to hair matrix carcinoma, that thirteen of our tumors were from both sweat glands and hair follicles, that it is quite possible that undifferentiated carcinomas of sweat glands may

of finely papillary growth clearly derived from the sweat ducts Babes and Kaufmann described cases, and the following is another example

Case VII (Mr A F MacLure's case)—For several months, a woman aged 60 had noticed a slowly enlarging hairless moist patch on her scalp, this showed a well defined circular area 1 centimetre in diameter in which the epidermis was replaced by a soft villous pink tissue. Sections of the excised area showed a finely papillary growth clothed by a double-layered epithelium resembling that of the sweat ducts (Figs 117-119). The subjacent dermis contained large dense collections of lymphocytes.

(ii) *Growth*—Most sweat-gland tumours grow slowly and non-invasively. A disorderly structure does not necessarily denote malignancy. Papillary or solid growths have often been dubbed "adenocarcinoma" because of their disorderly structure and the absence of a capsule, but they seldom recur after

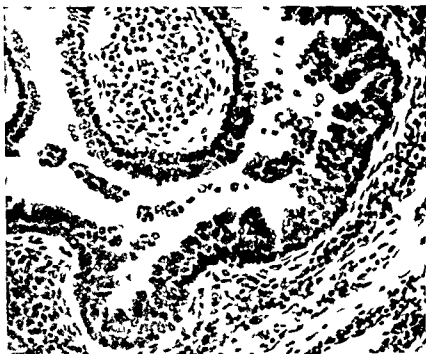


FIG 119—*Case VII* Sweat glandular papilloma of surface of scalp. Enlarged view of part of Fig 118 ($\times 250$)

removal. However, a few genuinely malignant infiltrating tumours have been observed, with occasional metastasis to the regional lymph glands (references by Gates *et al*).

(6) Tumours of other special glands

It is convenient to mention here the rare adenomas and adenocarcinomas of the ceruminous glands (Montpellier and Laffargue, Warren and Gates), and of the lachrymal and tarsal glands (Flick, Ziporkes, Tille and Leroux Robert). The lachrymal tumours often show a close structural resemblance to salivary tumours (Fig 120). For tumours of the lachrymal caruncle see Evans and of the lachrymal sac Penman and Wolff and Spratt.

the basal cell and glandular types of growth arising from the sub epidermal appendages of the skin. Many transitional and 'atypical' tumours occur, our

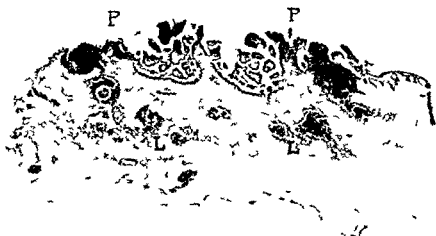


FIG 117—*Case VII* Sweat glandular papilloma of surface of scalp. General view showing replacement of epidermis by papillary growth (P) and collections of lymphocytes in dermis (L) ($\times 10$)

sub groups made according to the predominant structure in the individual tumours, have descriptive value but are arbitrary. It is noteworthy that the sweat glands and ducts can undergo squamous metaplasia in non neoplastic lesions (Fig 116)



FIG 118—*Case VII* Sweat glandular papilloma of surface of scalp. Details of Fig 117 note the double layer of epithelial cells ($\times 80$)

A very rare type of sweat glandular tumour remains to be mentioned. This takes the form of a replacement of the surface epidermis by a pink velvety layer

Structure (Figs 121 123)—The epidermis is thickened and the interpapillary processes broad and blunt. The cells, especially of the spinous layer, show great irregularity of size and shape, including giant or multinucleated forms. Mitotic figures are plentiful, and many of the nuclei are hyperchromatic or distorted. Large rounded pale or vacuolated cells, resembling those of Paget's disease, are often present. The surface may or may not show excessive keratosis. The dermis shows chronic inflammatory changes and abundant lymphoid and plasma cells.

The following are my personally studied cases

Case VIII—Male 70. Multiple patches on the back of many months' duration (Figs 121 and 122).

Case IX—Male 70. Single patch 2.5 centimetres in diameter on dorsum of forearm of 6 years' duration (Fig 123).

Case X—Male 55. Fair skinned man, always very sensitive to sunburn, has had many keratoses of the face for years. Plaque like rough area 2 centimetres in diameter developing behind ear for 2 years, failed to respond to repeated radium applications, therefore excised. Structure closely similar to that of Case IX.

(b) *Extra mammary Paget's disease*

Paget's disease of the nipple is described in Chapter 13. From time to time extra mammary lesions resembling the nipple disease clinically and more or less histologically have been described. The earliest reports were those of Paget himself, Crocker, and Rolleston and Hunt. Paget's original reference to chronic balanitis followed by cancer is cited in Chapter 13, and he too concurred in the diagnosis of Crocker's case of Paget's disease of the scrotum and penis. Rolleston and Hunt's case also was one of clinically typical Paget's disease of the pubic and scrotal skin, in which the epithelial cells formed 'psorospermoid bodies' resembling those described by Darier. For more recent reports of cases of extra mammary Paget's disease, see references by Inglis, Weiner, and Stout. Weiner pointed out that all acceptable examples of extra mammary Paget's disease were from the axillae or ano-genital regions, i.e. regions where apocrine glands occur.

With the recognition and naming of Bowen's disease, uncertainty arose as to the distinction between this and extra mammary Paget's disease. Some workers, e.g. Inglis, distinguish sharply between them mainly on histological grounds, others like Savatard regard them as identical, or at least as only forms of the same disease. For reasons already given in Chapter 13, I adopt the latter view. In my opinion, Bowen's disease and Paget's disease are not sharply separable histologically; each may show areas resembling the other, and in particular Bowen's disease often shows rounded pale or vacuolated cells indistinguishable from Paget cells. The predominance of such cells in Paget's disease of the nipple and the usually greater bulk of the epidermis and its more pleomorphic cytology in Bowen's disease, are not sufficient grounds for their sharp separation.

Stout has reviewed the few reported cases in which the picture of Paget's disease has been produced by growths possibly of the nature of amelanotic melanomas. 'It is suggested that these cases form a group of superficial slow growing naevo carcinomas with Paget-like characteristics which distinguish them from other melanomas. Should future work verify this, the conception of the essential unity of all forms of epidermal carcinoma *in situ* will not be invalidated, melanomas also are epidermal growths.'

(7) Intra epidermal carcinoma

Several related diseases which were formerly regarded as "pre cancerous dermatoses" are to be looked on rather as forms of intra epidermal carcinoma. These are Bowen's disease, Paget's disease, Queyrat's erythroplasia, and some cases of vulval leucoplakia or kraurosis. (References by Inglis, and Mackee and Cipollaro)

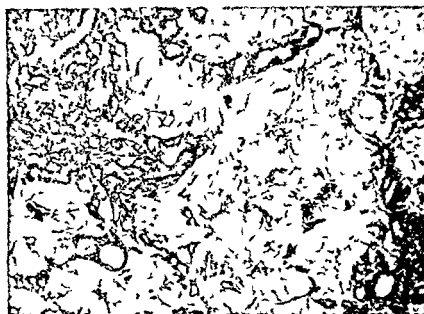


FIG 120—Adenoma of tarsal gland from a woman aged 40 the small well defined tumour had been present and slowly enlarging for 2 years ($\times 80$)

(a) Bowen's disease

Bowen's disease appears in any part of the skin of middle aged or elderly subjects of either sex as slightly raised reddish brown papular or plaque like lesions with crusted or eroded surfaces. The patches are often multiple in the



FIG 121—Case VIII Bowen's disease early lesion General view ($\times 8$)

affected region. They slowly enlarge and may coalesce to form extensive irregular areas. After a long period, usually many years, invasive squamous-cell carcinoma develops and metastasis occurs. Kuznitzky and Jacoby report a good example of this sequence.

(c) *Erythroplasia*

What has just been said of Bowen's and Paget's diseases applies also to Queyrat's erythroplasia or erythroplakia (references and illustrations by Mackee and Cipollaro). This is a rare affection of the glans and prepuce, vulva or mouth characterized by single or multiple shiny or velvety red areas in which frank carcinoma eventually develops. Microscopically the patches show epidermal thickening with "dystrophic" prickly cells. I can see no grounds for regarding this lesion as a distinct entity. Paget's "long-enduring balanitis" ending in cancer, later workers' Paget's disease" of the genitalia, "Bowen's disease" of the same regions, and "erythroplasia" are surely no more than variants of one thing.



FIG. 123.—Case 1A. Bowen's disease, later lesion, general view ($\times 8$)

(d) *Conclusion*

It remains only to add here that in some cases what appears to be vulval leucoplakia or kraurosis proves microscopically to be already intra-epidermal carcinoma resembling Bowen's disease (Chapter 32). This, then, is but another variant of the same disease. Different cases show somewhat different clinical and microscopical appearances according to site, causation, preceding or associated lesions, and individual peculiarities of the skin. Dermatologists have tried to define these differences, by the use of such words as "hyperkeratosis", "parakeratosis", "dyskeratosis" etc., while different appearances of the lesions have been over-emphasized by eponymous labels. But distinctions so created are quite arbitrary and without pathological value. For the pathologist there is only one entity: intra-epidermal carcinoma, which, like intra-duct carcinoma of the breast, may long remain confined within epithelial boundaries. Also like intra-duct carcinoma, intra-epidermal carcinoma shows many structural variations, but these do not denote distinct forms of tumour nor call for distinctive names.

REFERENCES

- Babes A (1928) *Virchows Arch*, 269, 809
 Baker A H and Hawksley L M (1931) *Brit J Surg*, 18, 415
 Beadles, C F (1894) *Trans Path Soc Lond*, 45, 176
 Benecke E (1931) *Frankfurt Z. Path.*, 42, 502
 BERESTON, E S, and NEY C (1941) Squamous cell carcinoma arising in a chronic osteomyelitis sinus tract with metastasis *Arch Surg* 43, 257 (A good review)
 Brown J B and McDowell F (1942) *Surg Gyn Obst* 74, 1128
 Burns E L (1935) *Arch Surg*, 30, 266
 Caylor H D (1925) *Ann Surg* 82, 164
 Cookson H A (1924) *Brit Med J* i, 363

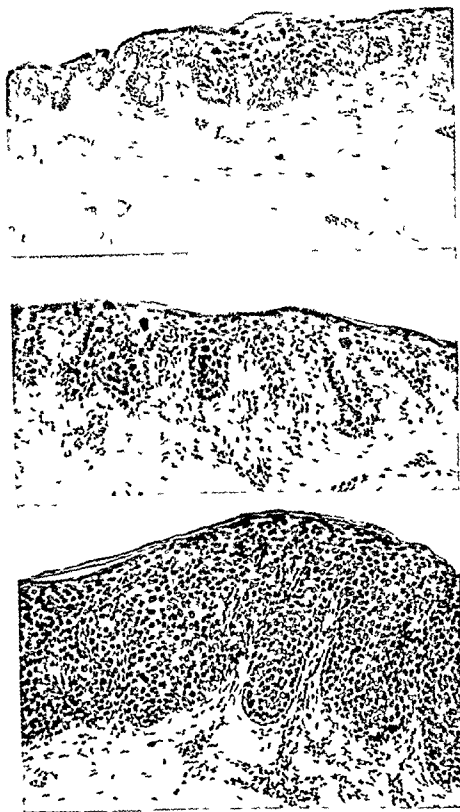


FIG 122 —Case VIII Bowen's disease early lesion Details of Fig 121 A = $\times 85$ B and C = $\times 144$

- Penman G G and Wolff E (1938) *Lancet* 1 1325
- PETROV N, and GLASUNOW, M (1933) 'Über die sogenannten Knochenendothelome und die primären epithelialen Knochengeschwülste' *Arch klin Chir* 175 589 (Includes a good review of the first 8 reported cases of basal cell carcinoma of the tibia)
- Phillips C (1942) *South Med J* 35 583
- Rehbock D J and Barber C G (1938) *J Bone Joint Surg*, 20 187
- Richter C S (1930) *Z Krebsforsch* 32 273
- Rolleston H D and Hunt E L (1897) *Trans Path Soc Lond* 48 211
- RONCHESE, F (1933) Multiple benign epithelioma of the scalp (turban tumors) *Amer J Cancer* 18 875 (A useful review)
- Ryrie B J (1932) *Brit Med J* 11 1000
- Savatard L (1924) *Brit Med J* 11 460
- Savatard L (1938) *Brit J Derm Syph*, 50 333
- Sheldon W H (1941) *Arch Path* 31 326
- Shrek R (1941) *Arch Path* 31 434
- Shrek R and Gates O (1941) *Arch Path*, 31, 411
- Sigel H (1937) *Amer J Cancer* 30 108
- Sikl H (1932) *Frankfurt Z Path* 43, 1
- Simard L (1938) *Amer J Cancer* 33 182
- Spratt C N (1940) *Arch Ophth*, 24 1237
- Stout A P (1938) *Amer J Cancer* 33 196
- Streitmann B (1946) *Klin Med* 1 486
- Taylor G W Nathanson J T and Shaw D T (1941) *Ann Surg* 113 268
- Thomas R G (1939) *Brit J Surg* 26 547
- Tillé H and Leroux Robert J (1938) *Bull Assoc franç Cancer* 27 596
- TREVES, N, and PACK, G T (1930) 'The development of cancer in burn scars' *Surg Gyn Obst* 51 749 (A valuable study and review)
- Vaughan K (1925) *Brit Med J* 11 495
- Warren S and Gates O (1941) *Amer J Path*, 17 821
- WARREN, S, and WARVI W H (1943) Tumors of sebaceous glands, *Amer J Path*, 19 441 (A useful review)
- WARVI, W N, and GATES, O (1943) Epithelial cysts and cystic tumors of the skin *Amer J Path* 19 765 (A useful review)
- Weiner H A (1937) *Amer J Cancer* 31 373
- Willis R A (1930) *J Coll Surg Austral* 2, 417
- Willis R A (1930) *Med J Austral* 11 87
- WILLIS, R A (1944 and 1945) 'The mode of origin of tumours', *Cancer Res* 1944 4, 630, and 1945 5 469 (The evidence for the field origin of skin tumours)
- Wilson J M (1941) *Arch Surg* 43 101
- Wolfort B and Sloane D (1938) *J Bone Joint Surg*, 20 1011
- Ziporkes J (1937) *Arch Ophth*, 18, 933

- COPELAND, M M, and MARTIN, H C (1932) Xeroderma pigmentosum, *Amer J Cancer* 16 1337
- COTE, F H (1936) Benign calcified epithelioma of the skin, *J Path Bact* 43 575
- Crocker H R (1888) *Trans Path Soc Lond* 40 187
- Dawson J W (1925) *Edinb Med J* 32 537 and 606
- Drabble J (1929) *J Compar Path and Ther* 42 40
- Drabble J (1929) *Austral Vet J* 5 71
- Eliason E L and McLaughlin C (1933) *Ann Surg* 97 947
- Emmel M W (1930) *J Amer Vet Med Assoc* 77 641
- Evans W H (1940) *Arch Ophth* 24 83
- Finnerud C W (1924) *J Amer Med Assoc* 82 775
- Fischer B (1913) *Frankfurt Z Path* 12 422
- Flick J J (1944) *Amer J Ophth* 27 362
- Flint E R and Gordon J (1928) *Brit J Surg* 16 321
- Fox R A (1943) *Arch Path* 36 195
- FRANSEEN, C C and TAYLOR, G W (1934) Arsenical keratoses and carcinomas *Amer J Cancer* 22 287 (A good review)
- GATES O WARREN S and WARVI W N (1943) Tumors of sweat glands *Amer J Path* 19 591 (A useful review with many references)
- Geschickter C F and Koehler H P (1935) *Amer J Cancer* 23 804
- Glasunow W (1933) *Frankfurt Z Path* 46 140
- Goldsmith W N and Freudenthal W (1935) *Proc Roy Soc Med* 28 1528
- HAAGENSEN C D (1931) Occupational neoplastic disease *Amer J Cancer* 15 641
- HAYTHORN S R (1931) Studies on the histogenesis of the so called basal-cell carcinoma *Amer J Cancer* 15 1969 (An excellent account with many fine illustrations)
- Holden E and Gray J W (1934) *J Bone Joint Surg* 16 401
- HUEPER W C (1942) *Occupational Tumors and Allied Diseases* Springfield
- Inglis K *References* Chapter 13
- Innes J R M and Whittick J W (1940) *J Compar Path and Ther* 53 115
- Kaufmann E (1929) *Pathology* p 2200 Translation by Reimann Philadelphia
- Kreibitz W (1931) *Frankfurt Z Path* 42 281
- KROMPECHER E (1900) Der drusenartige Oberflächeneithelkrebs *Carcinoma epitheliale adenoides* *Beitr path Anat* 28 1
- KROMPECHER E (1902) *Der Basalzellenkrebs* Jena
(Classics in the pathology of skin tumours)
- Kuznitzky E and Jacoby H (1938) *Arch Derm Syph* 38 191
- Lawrence K B (1941) *Arch Surg* 43 88
- Lohmer H *Reference* Chapter 7
- MacCormac H (1924) *Brit Med J* ii 457
- MACKLE G M, and CIPOLLARO A C (1937) *Cutaneous Cancer and Pre cancer* New York (A valuable monograph with many excellent photographs and microphotographs)
- McFarland J Ciccone E F and Gelehrter J (1935) *Amer J Cancer* 25 273
- Martin H E and Stewart F W (1935) *Amer J Cancer* 24 273
- Mathews F P (1937) *Arch Path* 23 399
- MOLESWORTH E H (1927) Rodent ulcer *Med J Austral* i 878 (An important clinical and pathological study stressing sunlight as a causative factor)
- Montgomery H (1928) *Arch Derm Syph* 18 50
- Montpellier J and Laffargue P (1938) *Bull Assoc franç Cancer* 27 774
- Mulzer P (1930) *Klin Wschr* 9 2086
- De Navasquez S (1941) *J Path Bact* 53 437
- Neve E F (1923) *Brit Med J* ii 1255
- Newland H (1936) *Med J Austral* ii 221
- Nicholson G W (1917) *J Path Bact* 21 287
- Nicholson G W (1923) *Guy's Hosp Rep* 73 298
- Niles H D (1931) *Amer J Cancer* 15 2341
- Oberling C Vermes E and Chevereau J (1938) *Bull Assoc franç Cancer* 27 373
- O Donovan N J (1926) *Lancet* ii 278
- Paul N and Inglis K (1927) *Brit J Derm Syph* 39 195

one third of the cases. About 6 per cent of oral cancers in betel chewers occur on the lips (Orr), many of these are on the mucous membrane of the inner surface of the lips near the angle of the mouth.

(a) Tobacco smoking

That pipe smoking can be causative seems probable from the records of cases in which cancer has developed just where long-standing irritative changes from an habitual position of the pipe has been present, and from the prevalence of cancer of the lip in women in communities where the women smoke pipes. Thus it is said that Irish peasant women and negro women who smoke clay pipes often get cancer of the lip (references by Hueper), and Ahlbom noted that 50 per cent of the lip cancers in Swedish women were in pipe smokers. The risk of pipe smoking with its tarry products, heat and mechanical irritation, might be suspected *prima facie*, and Flory and Roffo have shown that tobacco tar is indeed carcinogenic. Thus, there are good grounds for concluding that pipe smoking is a causative factor for lip cancer and that it probably acts by means of chemical carcinogens, perhaps aided by mechanical or thermal injuries to the tissues (see Chapter 4). The part played by cigarette-smoking is much more debatable, and the evidence inconclusive.

(b) Sunlight

Sunlight has been blamed as an important cause of lip cancer, e.g. by Haagensen and Molesworth. These workers point out that this factor would explain the sex incidence of the disease, its disproportionate frequency in farmers, fishermen and other outdoor workers, and its high frequency in sunny countries like Australia. Molesworth recorded that with rare exceptions his Australian cases showed clear evidence of chronic sunburn, often including keratoses of the lip and other parts of the face. The great preponderance of tumours of the lower lip is explained as due to direct exposure of its mucocutaneous junction to sunlight, while the corresponding part of the upper lip is relatively shaded. The proved importance of sunlight in the causation of skin cancer also makes a strong case for its importance in lip cancer.

(c) Exposure to tar, pitch or oil

This is certainly another causative factor in certain occupations (references by Hueper). A peculiar instance of such exposure is in the net fishers described by Shambaugh. These men, when mending their tar impregnated nets, have the habit of holding the tar smeared wooden needle between the lips. The lips visibly retain smudges of tar for long periods. Since Beck experimentally proved the carcinogenic properties of the tar mixture used by the fishers, the evidence is strong that the fairly frequent lip cancers encountered amongst them are due to this cause.

(3) Structure

Most of the tumours are of ordinary cornifying squamous cell type (Figs 12 and 124). A few of them show predominant "tubular acanthoma" or poorly differentiated anaplastic growth. Study of early tumours shows that they arise

CHAPTER 15

EPIDERMOID CARCINOMAS OF THE LIPS, MOUTH, PHARYNX AND LARYNX

THE EPITHELIAL tumours of the oropharyngeal region comprise the following

- (a) Papillomas of the surface epithelia
- (b) Epidermoid carcinomas of the surface epithelia
- (c) Tumours of the dental shelf tissues
- (d) Tumours of salivary and other glandular tissue

The surface papillomas are infrequent and show no specially notable features, tumours of the derivatives of the dental shelf are described in Chapter 16 and salivary glandular tumours in Chapter 17. The present Chapter is concerned with the epidermoid carcinomas of the surface epithelia. In different situations these growths differ somewhat in causation, structure and behaviour, yet they have much in common and are best considered together.

EPIDERMOID CARCINOMA OF THE LIPS

For good accounts of incidence, causation and pathology, see Lane Claypon (1930), Newell (1939) and Martin *et al* (1941). In analysing the properties of cancer of the lip, only growths of the muco-cutaneous junction should be considered. Basal cell growths of the labial epidermis should be excluded, since, as Newell's paper shows, these differ strikingly from epidermoid carcinomas in site and sex incidence.

(1) Age, sex and site incidence

The mean age of patients when they first come under observation varies in different series from 52 to 65 years, with a general average of about 57. Two-thirds of the cases are between 50 and 70 years of age. The mean age at death of fatal cases is 70. The disease is very rare in youth; New and Hertz reported it in a boy of 13 years.

Of Lane Claypon's collected 4,839 cases, 93.5 per cent were males, a sex ratio of 14 to 1. In Pack and Le Fevre's series the ratio was 16 to 1.

The lower lip is far more frequently affected than the upper, the percentages in the series of Lane Claypon, Newell and Martin *et al* being 94, 95 and 93 respectively. The disproportion is much less for females than for males; in women nearly one-quarter of the tumours are in the upper lip, but in men only 3.6 per cent of them (Lane Claypon). This difference points clearly to the operation of different causative factors in men and women. (See Ahlborn's (1936) work discussed later.)

(2) Causative factors

There is little or no evidence that syphilis, alcoholism and dental irritation are important causative factors. Non-syphilitic leucoplakia is present in nearly

The percentages of males in Lane Claypon's, Pack and Le Fevre's, and Morrow's series were 90, 87 and 84 respectively.

In nearly two thirds of the cases the tumours arise along the lateral margins of the tongue, the remainder on the dorsum, under-surface, base and tip in that order of frequency.

(2) Causative factors

Alcohol, tobacco, dental disease and hot food have often been blamed as causative, but, while any or all of these may indeed play a part, proof is difficult.



FIG. 125.—Diffuse spindle-celled growth at the invading edge of a carcinoma of the tongue ($\times 120$).

to obtain. The tongue holds third place in the list of sites of oral cancer in betel chewers. The palate and tongue are the two commonest sites of oral cancer in Indians who smoke cigars with the lighted end inside the mouth (Kini). The Plummer-Vinson syndrome as a precursor of female oral cancer generally is discussed later.

Syphilitic glossitis

This condition, usually with leucoplakia, is the most clearly established single causative factor in European males. Of course its frequency in different series of cases varies. Fournier's figure of 84 per cent was certainly an over-estimate, as his practice was principally amongst syphilitic patients; unselected series have shown serological or other evidence of syphilis in percentages ranging from 17 to 42 (Lund, Morrow). For the relationship between syphilis, leucoplakia and oral carcinoma, see Power, Lane-Clayton and Stewart.

from fields of predisposed tissue which include both epidermis and mucosa, and sometimes a tumour displays clear structural evidence of this dual origin (See Fig 12)

(4) Growth and metastasis

Many of the tumours grow slowly and metastasize late, following simple V shaped excision or effective radiational treatment of early tumours prognosis



FIG 124 —Spinous cells in carcinoma of lip ($\times 1000$)

is favourable But in a large proportion of cases the growths are of many months duration when advice is first sought and in some of these metastases are already present in the submaxillary or submental lymph glands (Newell) In late stages, metastases are common in lymph glands and blood borne metastases are not unusual Remote metastases were present in 4 of 14 necropsy cases recorded by Martin *et al* and in 2 of my 7 necropsy cases (Willis 1934, Cases 45 and 287)

EPIDERMOID CARCINOMA OF THE TONGUE

Good accounts include those of Power (1919), Lane Claypon (1930) and Morrow (1937)

(1) Age, sex and site incidence

The mean age of patients is about 54 and nearly two thirds of the cases are in the sixth and seventh decades The mean age of fatal cases is about 61 years The disease is rare in young people but has been seen occasionally in children and even in the newly born (Frank *et al* Salceby) New and Hertz reported patients of 13 and 22 years

Metastatic growths in the neck may be the first signs of small posterior lingual carcinomas. This applied to Cases 31, 122, 154 and 283 of my 1934 work, in three of which the primary growth remained undiscovered during life and was revealed only by careful necropsy. The earliest metastases are usually in the upper deep cervical lymph glands along the course of the great vessels, and, if the primary tumour is undiscovered, these metastases are apt to be misdiagnosed "branchial carcinoma". Contralateral metastases are not unusual. The cervical growths spread from gland to gland of the carotid chain, and eventually form large fused masses enveloping the vessels and frequently occluding or invading the jugular vein. Few advanced cases of lingual cancer are without multiple cervical metastases: these were present in 18 of 20 necropsy cases reported in my 1934 work.

(b) *Blood borne metastases*

These were present in 8 of my 20 necropsies (40 per cent), and Martin *et al* recorded the same percentage in 50 necropsies. The organs affected are most frequently the lungs and liver, but other sites include the myocardium, kidneys, adrenals, bones, spleen, muscles and skin (Fig. 126). Most cases with remote metastases show large cervical metastases with invasion of the jugular vein, Fleming however, reported a remarkable case in which there were numerous metastases in many organs but the cervical lymph glands were not affected.

EPIDERMOID CARCINOMA OF THE CHEEK, PALATE AND MOUTH FLOOR

(1) Age, sex and site incidence

In Europeans the average age is about 59, and half of the cases occur in the fifth and sixth decades (Martin and Pflueger). Carcinomas in betel-chewers and in the Indians who smoke cigars in the reversed position occur at earlier average ages, thus 44 per cent of Orr's cases were in the fifth decade and the mean age of Kim's cases was 42.5 years.

Martin and Pflueger's series of 99 cases of cancer of the cheek comprised 90 men and 9 women. Betel chewer's cancer also is usually commoner in men than in women (Orr), but the sex disparity is much less marked than in buccal cancer in Europeans, and it varies markedly in different communities. Betel cancer is particularly common among Filipino and Cingalese women, who suffer from it as much as or even more than the men (Maxwell, Vedder, Spittel).

In Europeans cancer affects the cheek, mouth floor and palate in that order of frequency. Betel chewer's cancer is most frequent on the cheek or lower jaw opposite the molar and premolar teeth where the quid is carried, but other parts of the oral cavity are also affected. Thus in Orr's series the sites were: cheek 296 cases, lower jaw 196, tongue 96, upper jaw 41, lips 40 cases. The distribution of oral cancers in an Indian community who smoked cigars with the lighted end in the mouth was: palate 52 cases, tongue 50, cheek 26, fauces and pharynx 14, jaw 13 (Kim).

(2) Causative factors

Unequivocal carcinogenic factors like the betel chewing or reversed

(3) Structure

Most of the tumours show cornifying squamous cell structure of varying degrees of differentiation (*see* Figs 13 and 126). A few tumours however, show marked anaplasia with loss of recognizable epidermoid characters (Figs 18 and 125). This is more frequent with growths of the base than with growths in other parts of the tongue. Occasional tumours of the base have the structure of 'lympho-epithelioma', more frequent in the nasopharynx (q.v.)



FIG 126 —Metastasis of cornifying epidermoid carcinoma of the tongue in adrenal gland ($\times 80$)

(4) Growth and metastasis

Carcinoma of the tongue is a much more malignant tumour than carcinoma of the lip. Growth is often rapidly invasive and early metastasis to the upper cervical lymph glands is frequent.

(a) Metastases in lymph glands

Many patients already have lymph nodal deposits when they are first seen. Early deposits are certainly embolic, for no tumour is demonstrable between the growth in the tongue and the glandular deposits and occasional cures have been obtained by local excision of the primary tumour and of the affected glands. The following case exemplifies this result.

Case 1—A woman 69 years of age presented herself in 1928 with an ulcerated carcinoma 1 centimetre in diameter on the left lateral border of the anterior part of the tongue and a palpably enlarged submaxillary lymph gland. Excision of the primary tumour along with a large part of the affected half of the tongue was performed and the lymph glands on the left side were removed. Microscopically both showed cornifying squamous-cell carcinoma. The patient remained well until 1945 when at the age of 86 she died of broncho-pneumonia.

is remarkable in that it predominates in women, 90 per cent of Ahlbom's cases and all of the 29 patients seen by Pilcher were women.

While tumours of any structural variety may occur in any part of the pharynx or fauces, particular variants predominate in particular situations. Most carcinomas of the tonsils, fauces and lower part of the pharynx are squamous-celled, while in the nasopharynx the so-called lympho-epitheliomas and transitional cell carcinomas predominate. The commonest site of nasopharyngeal growths is in the lateral wall close to the Eustachian orifice so that unilateral deafness is a frequent early symptom. The pyriform fossae are the commonest sites of hypopharyngeal growths. Carcinomas of the Eustachian tube and middle ear have been described by Stewart and Lieber, and by Rosenwasser.

(2) Causative factors

The incrimination of external agents such as alcohol, tobacco or hot foods is even more uncertain than in tumours of the oral cavity. Digby *et al* suggested that the very high incidence of nasopharyngeal carcinoma at a relatively early age in Hong Kong Chinese and other orientals might be due to the prolonged inhalation of smoke from lamps, fires and tobacco in the badly ventilated native houses but of course this is uncertain. There is no evidence that syphilis is important in causation. Chronic tonsillitis is thought to predispose to tonsillar carcinoma (Cappell) and many of the reported cases of middle ear carcinoma have given histories of long-standing infection (Rosenwasser).

The Plummer-Vinson syndrome

As a precursor of carcinoma of the pharynx, and also of the mouth and oesophagus in women, this condition has been emphasized particularly by Ahlbom. This syndrome, which is nearly confined to women, consists of dysphagia and anaemia, often accompanied by achlorhydria. The dysphagia appears to be due to atrophic changes in the oral and pharyngeal mucosa, perhaps with accompanying reflex muscular spasm. Several patients with this syndrome and with multiple carcinomas of the oral cavity arrested the attention of Swedish workers, and search then showed that the syndrome or simple achlorhydria was present in about 70 per cent of cases of oropharyngeal or oesophageal cancer in Swedish women and that in cases of post-cricoid carcinoma the proportion was 90 per cent. In Sweden, oropharyngeal carcinoma occurs with about equal frequency in men and women, and it is clear that alcohol and syphilis are relatively unimportant factors in causation and that the most important single predisposing factor is the nutritional disorder which expresses itself as either the Plummer-Vinson syndrome or as simple achlorhydria. The relative importance of this factor in other communities has still to be decided.

(3) Structure

Most pharyngeal and faucial growths are epidermoid carcinomas of the well-known type, though many of them are structurally atypical and anaplastic (Willis 1930). In 1921 Regaud and Schmincke proposed the name 'lympho-epithelioma' to distinguish a group of highly radio-sensitive tumours, most frequent

cigar smoking of oriental communities are seldom identifiable in European cases. In their series of cheek cancers Martin and Pflueger found that signs of chronic irritation or leucoplakia were frequently present but as with other oral cancers the degree of importance to be attached to particular factors such as dental irritation, syphilis, smoking and the Plummer-Vinson syndrome remains uncertain.

The carcinogenic substance responsible for betel-chewer's cancer is still to be identified. The quids consist of mixtures of buyo leaves, Areca or betel nuts, slaked lime, tobacco and spices. The composition of the quid varies in different countries and districts, and this probably accounts for the marked differences in the frequency of betel cancer in different localities. Thus, betel-chewing is a common habit but betel cancer is of low incidence in Formosa, Guam and the Dutch East Indies, while in Madras, Malabar Coast, Travancore, Ceylon and the Philippines betel cancer is a very frequent, in some localities the most frequent kind of malignant disease. For further discussion see Khanolkar, 1944.

(3) Structure and metastasis

The tumours are of cornifying epidermoid type, with varying degrees of differentiation. Highly anaplastic growths are rare. In their local spread and their metastasis these tumours generally resemble lingual cancers but are on the average slightly less malignant. In Martin and Pflueger's 99 cases metastases developed during the course of the disease in 51, in all but 11 of which the metastases appeared to be restricted to the submaxillary lymph nodes.

EPIDERMOID CARCINOMA OF THE TONSILS AND PHARYNX

For useful accounts see Trotter (1911), New (1922), Quick and Cutler (1927), Willis (1930), New *et al* (1932), Ahlbom (1936), Cappell (1938), and Godfredsen (1944).

(1) Age, sex and site incidence

As with the oral carcinomas, more than half of the pharyngeal carcinomas occur in the sixth and seventh decades. The age incidence is related to the type of growth, those of the 'lympho-epithelioma' type occurring earlier than those of squamous cell type. In Godfredsen's series of over 400 nasopharyngeal tumours the average age of patients with carcinomas was 51 years and of those with 'sarcomas' (mainly lympho-epitheliomas, no doubt) 46 years. Three of Cappell's 12 lympho-epithelioma cases were under 30 years old, namely 21, 23 and 25, and he refers also to cases in children aged 8 and 12. The mean age at death of 27 cases of squamous cell carcinoma of the pharynx on which I performed necropsies was 64. Digby *et al* reported 114 cases of nasopharyngeal carcinoma in Chinese in Hong Kong; these showed a relatively early age incidence, the peak of the distribution curve being in the fourth decade.

Squamous cell carcinomas of the pharynx and tonsil show a decided preponderance of males: my 27 necropsy cases comprised 20 men and 7 women. In Pack and LeFevre's series the sex ratio for tonsillar carcinomas was 10 to 1. Lympho-epitheliomas show a less unequal sex incidence. Post-cricoid carcinoma ✓

the neck as well as blood borne metastases, Godtfredsen recorded distant metastases in 19 per cent of his entire series, in 27.5 per cent of his fatal cases, and in 18 of 47 necropsies (38 per cent)

EPIDERMOID CARCINOMA OF THE LARYNX

An early but good account of laryngeal cancer was that of Butlin (1883), see also Thomson and Colledge (1930) on the clinical aspects, and Kaufmann (1929) on the pathological aspects of the disease

(1) Age, sex and site incidence

In a consecutive series of 70 patients with laryngeal carcinoma examined by Thomson and Colledge, 30 were in the sixth decade. The mean age of Pack and Le Fevre's series was 57. The mean age of my 11 necropsy cases was 62. New and Hertz saw the disease in a boy of 15. All recorded series show a great predominance of males over females, usually in a ratio of about 10 to 1. The Registrar General's 1931 report showed that fatal carcinoma of the larynx, like that of the mouth and pharynx, showed a decided class gradient amongst males, being highest in the unskilled classes, but, unlike buccal and pharyngeal cancer, laryngeal showed no class gradient in women "suggesting that the factors responsible for the excess of cancer of this site amongst unskilled males are directly associated with occupation."

Intrinsic carcinoma of the larynx arises most commonly in the vocal cords, less often in the ventricles or below them. Cancers of the epiglottis, arytenoid region or aryepiglottic folds are uncommon.

(2) Causative factors

Over-use of the voice, syphilis, tobacco, alcohol, and various occupational dusts and fumes (references by Hueper) have all been suggested as possible causative factors, but the evidence is inconclusive. Jackson believed that 65 per cent of laryngeal cancers were preceded by "vocal abuse", but Thomson and Colledge failed to find pre-cancerous conditions in most of their cases. The great predominance of the disease in males, and the decided class gradient in males not shared by females, point strongly to occupational factors in causation and inhaled substances may well be the main agents.

Relation of papilloma to carcinoma

Papillary growths of the larynx are of the following kinds: (a) Multiple papillomas in children (examples by Bland Sutton, Kaufmann, and Ferguson and Scott) numerous cauliflower-like growths spring from the mucosa, and may fill the larynx and cause suffocation. Bland Sutton mentioned the spontaneous disappearance of such growths following tracheotomy. Hitz and Oesterlin saw a child in whom multiple bronchial implants developed in the lungs, but invasive carcinoma has not been observed to supervene in this peculiar disease. (b) Non-invasive but often recurring multiple or single papillomas in adults, after repeated recurrences some of these show invasive carcinoma. (c) Papillary

in the nasopharynx, possessing a rather diffuse structure with lymphoid cells intimately mixed with poorly differentiated carcinomatous tissue. Although Schmincke and Regaud are usually credited as the first to segregate this group of tumours Trotter had clearly described them clinically in 1911, designating them endotheliomas. Schmincke's name lympho-epithelioma has been widely adopted; the tumours have been divided into Regaud and Schmincke types, and there has been much discussion as to the interrelationships of 'lympho-epithelioma', Ewing's 'transitional cell carcinoma' and squamous cell carcinoma of ordinary structure (see New, Ewing, Quick and Cutler, Harvey *et al*, and Cappell). To add to the confusion some writers e.g. Godtfredsen, group the lympho-epitheliomas as sarcomas.

In my opinion the controversy is largely over names: the various names denote, not distinct entities, but only variants of the entity *epidermoid carcinoma of the pharynx*. The close admixture of lymphoid cells with certain carcinomas arising in the lymphoid areas of the pharynx and throat does not distinguish them sharply from other carcinomas of the region. Histologists are still uncertain of the precise relationships of epithelium and lymphoid tissue in the tonsils and thymus—whether the close association of the two tissues means a genetic relationship or an inductive or attractive effect of one on the other. Whatever the interpretation it is not surprising that an association characteristic of the normal tissue of the region should sometimes be perpetuated in its tumours. Moreover, lymphoid infiltration is not peculiar to pharyngeal tumours but is a distinctive feature of some other kinds of tumours e.g. seminoma. From my own examinations of pharyngeal tumours, and from my study of the micro figures in the papers of the various authors already cited especially those of Harvey *et al*, Cappell and Digby *et al*, I am satisfied that the lympho-epitheliomas are anaplastic carcinomas, that between well cornified squamous cell growths and the most sarcoma-like lympho-epitheliomas tumours of every gradation of structure can be found, and that a wide range of structure can be found also in some individual tumours (see Fig. 127).

(4) Growth and metastasis

Pharyngeal and tonsillar carcinoma resembles lingual carcinoma in its powers of invasion and metastasis. Direct extension of the nasopharyngeal tumours to the base of the skull often occasions early involvement of one or more of the cranial nerves producing a variety of symptoms and syndromes which have been fully described by New and by Godtfredsen. Dissemination to the upper deep cervical lymph glands occurs early and in a high proportion of cases. Enlarged glands were present in 75 per cent and were the first symptom in 32 per cent, of Godtfredsen's patients. Cervical metastases were present in 24 of my 27 necropsy cases (89 per cent). Many workers have described cases in which large cervical growths secondary to small symptomless tumours of the tonsil or pharynx were mistaken for primary lymph gland or branchial tumours (see below).

Distant blood borne metastases, usually consequent on invasion of the jugular vein from the enveloping cervical growths, are present in about 40 per cent of fatal cases e.g. in 11 of my 27 necropsies. The organs most frequently affected are lungs, liver, kidneys and bones. Including lymph nodal deposits beyond

In 7 cases the primary sources of the large cervical growths were not discovered during life and in an eighth case the main symptoms had been caused by cerebral metastases of a small pharyngeal carcinoma which was disclosed only by necropsy. The misdiagnoses of the cervical tumours included 'branchiogenic carcinoma', 'endothelioma' and 'lymphosarcoma' of cervical lymph glands. McWhorter, Hudson Graff, Humberl and others have also commented on the frequency of carcinomatous cervical growths of clinically undetermined source, only careful necropsy can reveal the origin of many of these.

CARCINOMAS OF BRANCHIAL CYSTS

The foregoing facts show that a clinical or biopsy diagnosis of "branchiogenic carcinoma"—a diagnosis usually made merely because no primary source has been discovered—is valueless. Only complete and careful necropsy, to exclude primary tumours in all possible sites, can identify a cervical growth as of branchial origin. Cases like those of Lillie *et al*, Oliver, and many others can be dismissed. My series of 64 necropsies, referred to above, included 2 cases of possible branchial carcinoma. In both cases there were large upper deep cervical epidermoid carcinomas and thorough post-mortem examination failed to reveal any primary growth in the upper alimentary and respiratory passages or elsewhere. Even in these cases, however, the diagnosis is not certain, for the large solid growths had obliterated any evidence there may formerly have been of their origin in cysts and a salivary origin could not be excluded. In the following case the diagnosis of carcinoma of a branchial cyst seems very probable, though again not quite certain.

Case II—In 1937 a woman of 25 had had an inflamed left upper cervical swelling incised. Subsequently the swelling fluctuated in size but began to enlarge steadily early in 1940. In October 1940 the tumour occupying the usual position of a branchial cyst was removed. This was a well defined apparently encapsulated ovoid mass 5 centimetres by 3.5 centimetres consisting of firm and friable white growth interspersed by cystic spaces the structure suggesting origin of the growth from the cyst walls. Microscopically the growth was a diffuse epidermoid carcinoma mingled with plentiful lymphocytes (Fig 127). Pathological diagnosis carcinoma of a branchial cyst or metastatic carcinoma in a branchial gland. Careful and repeated examination of the patient failed to disclose any primary growth in the oral nasal or pharyngeal cavities. The patient remained well until April 1941 when recurrent growth appeared in the neck at the site of the former tumour. This steadily extended and finally invaded the floor of the mouth the left tonsillar region and the base of the tongue over a wide area. The patient died in October 1942 at the age of 30. Necropsy showed a large mass of growth in the left side of the neck containing a sloughing cavity continuous with extensive ragged ulceration of the floor of the mouth and tonsillar region. Some discrete deposits of growth were present in lymph glands in both sides of the neck. There were no growths in any other organs.

The youth and history of this patient, the situation and structure of the initial cervical growth and the prolonged absence of any sign of a primary growth in the oropharyngeal passages, although this was carefully searched for, all support the diagnosis of carcinoma in a branchial cyst. There seemed little doubt that the recurrent growth ulcerated only secondarily into the mouth and tonsil region but the possibility that a small undiscovered primary growth in this region may thereby have been submerged cannot be excluded.

carcinomas clearly invasive and malignant *ab initio*. In my opinion, no sharp distinction can be made between (b) and (c), papillary growths of the larynx like those of most other sites show a wide range of behaviour and there is no clear line of demarcation between the benign and the malignant. I have seen several cases in which repeated removal of histologically 'benign' papillomatous growths has eventually been followed by carcinoma and I believe that all papillary growths in the larynx should be looked upon as potentially cancerous.

(3) Structure

Almost all laryngeal carcinomas are of the ordinary cornifying epidermoid type. adenocarcinomas are very rare. Many of the tumours show papillary patterns especially in their early stages. Lympho epithelioma does not occur ✓ in the larynx.

(4) Growth and metastasis

Laryngeal carcinoma usually grows slowly and metastasizes late. The disease may run a very prolonged course, of 8 or 10 years or longer. The growth, commencing usually on one cord, first spreads horizontally in the cord and often extends across the anterior commissure to the opposite cord. Later it may spread in a vertical direction to the base of the epiglottis or to the subglottic area. The laryngeal cartilages act as barriers to the tumour and invasion of the walls of the organ is usually slow. The earliest part to be penetrated is often the anterior part of the crico thyroid membrane.

As long as the tumour remains confined to the interior of the larynx, metastasis seldom occurs but once it has traversed the wall to reach the peri laryngeal tissues metastases often appear promptly in the neighbouring deep cervical lymph glands. The disease often proves fatal however before metastases have developed, deposits were present in lymph glands in only 4 of my 11 necropsy cases. Remote metastases are rare but have been recorded in liver, lungs and other organs.

GENERAL SUMMARY OF THE METASTASIS OF EPIDERMOID CARCINOMATA OF THE HEAD AND NECK

In 1930 1934 and 1941 I recorded studies of the necropsy findings in 64 consecutive cases of epidermoid carcinoma of the facio cervical region. The primary sites were skin in 6 cases, lip 7 tongue 20, tonsil 5 palate 2, pharynx 17, larynx 3 maxillary antrum 1 alveolus 1 and in 2 cases probably branchial cysts. Metastases were present in the cervical lymph glands in 51 cases (80 per cent). Invasion of the main cervical veins, usually the internal jugular vein was found in 30 cases (46 per cent). Remote visceral metastases were found in 25 cases (39 per cent) in all but one of these tumour invasion of cervical veins was present while in only 6 of the 30 cases with invaded veins were remote metastases absent. These facts clearly show the blood borne origin of these metastases. The organs affected were lungs in 19 cases liver 14 kidneys 8 bones 5, myocardium 4 adrenals 4 thyroid 3 spleen 2 pancreas 2 voluntary muscles 2 and stomach, intestine brain bladder and gall bladder each in one case.

growth, if this has extended widely, conclusive proof of its branchial origin may still be unobtainable even at necropsy

EPIDERMOID CARCINOMAS OF THE OROPHARYNGEAL REGION IN ANIMALS

Feldman gives references to scattered records of oral, pharyngeal or laryngeal carcinoma in the horse dog cat, wolf, bear and fowl. The most frequent of these were carcinomas of the gums in horses, and of the tonsil or pharynx in dogs. Of 67 carcinomas of dogs studied by Rudduck and me, 12 were epidermoid carcinomas of the oral cavity arising in the gums in 2 cases and in the tonsils in 10 cases. We reported two of the tonsillar tumours in 1938. Withers also has described carcinoma of the tonsil in the dog. Like its human counterpart, this tumour is prone to produce large metastatic growths in the cervical lymph glands while the primary tumour remains small. Steiner *et al* reviewed the few recorded cases of carcinoma of the tongue in animals, and added two examples of this disease in monkeys.

REFERENCES

- Ahlbom H E (1936) *Brit Med J* ii 331
 Beck S (1938) *Brit Med J* ii 1313
 Bland Sutton J (1922) *Tumours Innocent and Malignant* p 337 London
 Butlin H T (1883) *Malignant Disease of the Larynx* London
 CAPPELL D F (1938) The pathology of nasopharyngeal tumours, *J Laryng*, 53, 558
 (A well illustrated account especially of lympho-epithelioma)
 Digby K H, Lai Fook W and Yeung Tsaw Che (1941) *Brit J Surg*, 28, 517
 Ewing J (1929) *Amer J Path* 5 99
 Feldman W H (1922) *Neoplasms of Domesticated Animals* p 292 Philadelphia
 Ferguson C F, and Scott H W (1944) *New England J Med*, 230 477
 Fleming W E (1940) *Med J Austral*, i 191
 Flory C M (1941) *Cancer Res* 1, 262
 Frank L W, Enfield C D and Miller A J (1936) *Amer J Cancer* 26, 775
 GODTFREDSEN E. (1944) Ophthalmologic and neurologic symptoms of malignant nasopharyngeal tumours *Acta Otolaryng*, Supp 59 (A valuable monograph with special emphasis on the clinical aspect. The author regards the more anaplastic growths as sarcomas.)
 GRAFF, S (1934) Über die bösartigen Geschwülste und geschwulstähnliche Neubildungen des Epipharynx *Beitr path Anat*, 94, 276 (A good account of small symptomless metastasizing nasopharyngeal carcinomas and of the diagnostic errors they cause.)
 Haagenensen C D (1931) *Amer J Cancer* 15, 641
 Hamperl H (1939) *Virchows Arch* 304 34
 Harvey W F, Dawson E K and Innes J R M (1937) *Edinb Med J*, 44 549
 Hitz H B and Oesterlin E (1932) *Amer J Path*, 8 333
 Hudson R V (1926) *Brit J Surg* 14 280
 Hueper W C (1942) *Occupational Tumors* Springfield Ill
 Jackson C (1923) *Ann Surg* 77, 1
 Kaufmann E (1929) *Pathology* translation by Reimann pp 320-326 Philadelphia
 Khanolkar V R (1944) *Cancer Res* 4 313
 Kini M G (1944) *Indian Med Gaz* 79 572
 LANE CLAYTON, J E (1930) Cancer of the lip tongue and skin *Rep Publ Health Med Subj* No 59 London (A valuable statistical study of the massed figures of many collected series with many references.)
 Lillie R D, Cox O H, and Teufel W C (1934) *Amer J Path* 10 97

I have yet to see a completely acceptable case of branchiogenic carcinoma, or indeed a completely acceptable report of such a case. While it is very probable



FIG. 127.—*Case II*. Carcinoma of lympho-epithelial type probably arising in a branchial cyst. Note diffuse structure, patchy incomplete cornification and admixture of lymphocytes ($\times 120$).

that this tumour does occasionally occur, it is certain that the great majority of tumours so designated are metastases from undetected primary growths elsewhere. Furthermore, as *Case II* just described shows, even in a case of genuine branchial

CHAPTER 16

TUMOURS DERIVED FROM THE EPITHELIUM OF THE DENTAL LAMINA

THE DEVELOPMENT OF THE DENTAL LAMINA AND TOOTH GERMS

A KNOWLEDGE of the development and fate of different parts of the dental lamina is essential to an understanding of the origin of the epithelial tumours and tumour-like malformations of the jaws

A tooth is a compound structure derived from two distinct embryonic tissues. The enamel cap of the tooth is an epithelial derivative of the dental lamina, which grows from the lining of the embryonic buccal cavity into the substance of the jaw. All other parts of the tooth—dentine, cementum and pulp—are derived



FIG 128 —Vertical section through a tooth germ of a 15 weeks foetus showing oral mucosa (O) dental lamina (D) and enamel organ (E) with stellate reticulum ($\times 60$)

from the embryonic mesenchyme. The outgrowth of the dental lamina commences in the fifth week, as it extends into the mesenchyme of the jaw, it develops two successive series of bud like thickenings, the first rudiments of the deciduous and permanent teeth. Each epithelial tooth germ or 'enamel organ' enlarges and grows deeper into the jaw and its attachment to the dental lamina becomes constricted. At the same time its deep surface becomes indented by a condensed mass of mesenchyme so that the enamel organ is now bell shaped, forming a thick epithelial cap over the papilla (Fig 128). This cap consists of three zones—(i) the *internal enamel epithelium*—a layer of tall columnar cells or *ameloblasts*

- Lund C C (1933) *New England J Med* 209 131
- Martin H MacComb W S and Blady J V (1941) *Ann Surg* 114 226
- Martin H E and Pfueger O H (1935) *Arch Surg* 30 731
- Maxwell J L (1924) *Br Med J* i 729
- McWhorter J E (1929) *Ann Surg* 90 1
- Molesworth E H (1934) *Derm Wschr* 99 945
- Morrow A S (1937) *Ann Surg* 105 418
- New G B (1922) *J Amer Med Assoc* 79 10
- New G B Broders A C and Childrey J H (1932) *Surg Gyn Obst* 54 164
- New G B and Hertz C S (1940) *Surg Gyn Obst* 70 163
- Newell E T (1939) *Arch Surg* 38 1014
- Oliver R L (1935) *Amer J Cancer* 23 16
- ORR, J M (1933) Oral cancer in betel nut chewers in Travancore *Lancet* ii 575
- Pack G T and Le Fevre R G (1930) *J Cancer Res* 14 167
- Pitcher R (1937) *Brit Med J*, i 13
- POWER D A (1919) On cancer of the tongue *Brit J Surg* 6 336 (A good discussion of causative factors, and an interesting historical outline)
- Quick D and Cutler M (1927) *Surg Gyn Obst* 45 320
- Roffo A H (1939) *Z Krebsforsch* 49 588
- Rosenwasser H (1940) *Arch Otolaryng* 32 38
- Rudduck H B and Willis R A (1938) *Amer J Cancer* 33 205
- Saleeby G W (1940) *Amer J Cancer* 38 257
- Schmincke A (1921) *Beitr path Anat* 68 161
- Shambaugh P (1935) *J Amer Med Assoc* 104 2326
- Spiittel R L (1923) *Brit Med J* ii 632
- Steiner P E Kluyer H and Brunschwig A (1942) *Cancer Res* 2 704
- Stewart H L and Lieber M M (1940) *Arch Path* 30 518
- STEWART M J (1931) Pre-cancerous lesions of the alimentary tract, *Lancet* ii 565
(Contains a valuable brief review of some of the causative factors in oral cancer)
- Thomson, St C and Colledge L (1930) *Cancer of the Larynx* London
- Trotter W (1911) *Brit Med J* ii 1057
- Vedder E B (1927) *J Amer Med Assoc* 88 1627
- WILLIS R A (1930) Epidermoid carcinoma of the head and neck with special reference to metastasis *J Path Bact* 33 501
- Willis R A (1934) *The Spread of Tumours in the Human Body* London
- Willis R A (1941) *Med J Austral* ii 258
- Withers F W (1939) *J Path Bact* 49 429

are visible in the dentine of a growing tooth, an increasingly wide calcified zone and a narrow uncalcified zone adjacent to the layer of odontoblasts. As the dentine increases in thickness, the odontoblasts recede, and finally attain their permanent position around the periphery of the connective tissue pulp. A thin layer of bony tissue or *cementum* later develops on the outer surface of the root dentine, at the neck of the tooth there is a junction of cementum and enamel. These relationships are of interest in interpreting the structure of the odontomes. Study of these growths confirms the impression, gained from embryological research, that the formation of odontoblasts and dentine is dependent on the presence of enamel-organ epithelium (*see* Mummery, and Huxley and De Beer).

In Chapter I it was pointed out that, in tissues the histological differentiation of which is not completed before birth, tumour-like malformations may result from postnatal disturbances of growth. This is particularly relevant for the tooth formative tissues, adulthood of which is not attained until eruption of the permanent teeth is complete. The epithelial residues of the enamel organ and of the dental lamina are plentiful around unerupted teeth, and may help to determine the direction of eruption (Mummery), inflammatory or nutritional disturbances may readily be conceived to induce proliferative changes or cyst formation in these residues during childhood or adolescence. So also in the young growing tooth in which active formation is still in progress, local infective or other disturbances may well evoke overgrowth or dislocation of enamel, dentine or cementum. These theoretical deductions are supported by study of the structure of odontomes, cysts and 'adamantinomas', and especially by the fact that most of these abnormalities appear early in life.

CLASSIFICATION AND ORIGIN OF DENTAL EPITHELIAL TUMOURS

As in so many other special fields of pathology, there has been needless elaboration of the classification and naming of the malformations, cysts and tumours connected with the tooth formative tissues. In my opinion, the only essential subdivisions of all of these lesions are the following

- (a) '*Adamantinoma*' or '*ameloblastoma*' is a true neoplasm derived from the epithelial residues of the 'enamel organ', the developing tissues of which the tumour structurally resembles. The old name 'epithelial odontome' is fortunately almost obsolete. This tumour is unrelated to the odontomes proper. The current names, '*adamantinoma*' and '*ameloblastoma*', are also misnomers, for the tumours do not arise from ameloblasts and do not form enamel (*see below*).
- (b) *Intra alveolar epidermoid carcinoma* is carcinoma of the ordinary squamous cell type, unconnected with the epithelium of the gums and arising in the substance of the jaw. Its origin must be from the paradental epithelial residues, and in view of its structure and its distinction from adamantinoma, we may suspect its source to be squamous-cell residues of the dental lamina rather than the residues of the tooth-germs.
- (c) *Odontomes* are benign tumour like malformations in which varying mixtures of tooth tissues proper—enamel, dentine and cementum—

in contact with the papilla (ii) the *external enamel epithelium* a superficial layer of small cuboidal cells on the convex aspect of the enamel organ and (iii) an intervening zone of shrunken epithelial cells connected only by long processes and elsewhere separated by clear intercellular fluid, forming the *stellate reticulum* or *enamel pulp*. Only the first of these zones, the layer of ameloblasts, will produce ✓

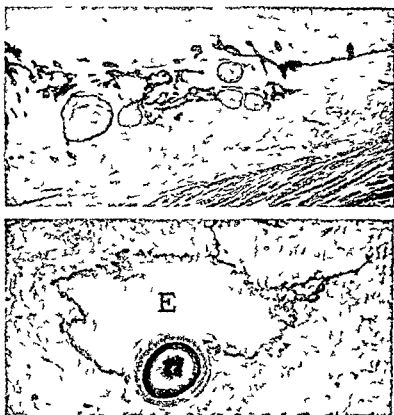


FIG 129 (a) and (b) —Horizontal sections through jaw of a 6-months foetus (a) at a plane just beneath the gum to show epithelial remains of the dental lamina including cornified pearls (b) at a plane through the summit of a tooth to show the great amount of non-enamel formative epithelial reticulum (F) around the tooth ($\times 40$)

the enamel of the developed tooth. the remainder of the enamel organ at this stage by far its bulkiest part will not form enamel but will persist as the para dental epithelial residues or sheath of Hertwig in the periodontal membrane ✓ around the fully formed tooth. Epithelial residues of the dental lamina itself also persist in the connective tissues around the summits of the developing teeth partly in the form of rounded cornified islands or epithelial pearls (Fig 129) these are visible in infants as nodules under the gums the so called 'glands of Serres'. It is from these various epithelial residues that epithelial tumours and cysts within the jaws arise.

The dentine of the developing tooth is produced by a layer of specialized mesenchymal cells the *odontoblasts* which arise at the periphery of the dental papilla adjacent to the ameloblasts. The dentine appears between the ameloblasts and the odontoblasts as a layer which gradually thickens. Two distinct zones

are visible in the dentine of a growing tooth, an increasingly wide calcified zone and a narrow uncalcified zone adjacent to the layer of odontoblasts. As the dentine increases in thickness, the odontoblasts recede, and finally attain their permanent position around the periphery of the connective tissue pulp. A thin layer of bony tissue or *cementum* later develops on the outer surface of the root dentine, at the neck of the tooth there is a junction of cementum and enamel. These relationships are of interest in interpreting the structure of the odontomes. Study of these growths confirms the impression, gained from embryological research, that the formation of odontoblasts and dentine is dependent on the presence of enamel organ epithelium (see Mummery, and Huxley and De Beer).

In Chapter I it was pointed out that, in tissues the histo-differentiation of which is not completed before birth, tumour-like malformations may result from post-natal disturbances of growth. This is particularly relevant for the tooth-formative tissues, adulthood of which is not attained until eruption of the permanent teeth is complete. The epithelial residues of the enamel organ and of the dental lamina are plentiful around unerupted teeth, and may help to determine the direction of eruption (Mummery), inflammatory or nutritional disturbances may readily be conceived to induce proliferative changes or cyst formation in these residues during childhood or adolescence. So also, in the young growing tooth in which active formation is still in progress, local infective or other disturbances may well evoke overgrowth or dislocation of enamel, dentine or cementum. These theoretical deductions are supported by study of the structure of odontomes, cysts and 'adamantinomas', and especially by the fact that most of these abnormalities appear early in life.

CLASSIFICATION AND ORIGIN OF DENTAL EPITHELIAL TUMOURS

As in so many other special fields of pathology, there has been needless elaboration of the classification and naming of the malformations, cysts and tumours connected with the tooth-formative tissues. In my opinion, the only essential subdivisions of all of these lesions are the following

- (a) '*Adamantinoma*' or "*ameloblastoma*" is a true neoplasm derived from the epithelial residues of the "enamel organ", the developing tissues of which the tumour structurally resembles. The old name '*epithelial odontome*' is fortunately almost obsolete, this tumour is unrelated to the odontomes proper. The current names "*adamantinoma*" and '*ameloblastoma*', are also misnomers, for the tumours do not arise from ameloblasts and do not form enamel (see below).
- (b) *Intra alveolar epidermoid carcinoma* is carcinoma of the ordinary squamous cell type, unconnected with the epithelium of the gums and arising in the substance of the jaw. Its origin must be from the paradental epithelial residues, and in view of its structure and its distinction from adamantinoma we may suspect its source to be squamous cell residues of the dental lamina rather than the residues of the tooth germs.
- (c) *Odontomes* are benign tumour-like malformations in which varying mixtures of tooth tissues proper—enamel dentine and cementum—

are present. These tissues are usually disorderly in arrangement and do not form properly developed teeth, though teeth may be associated with or incorporated in them.

- (d) *Epithelium lined cysts* in the jaws are formed in several different ways and of course are not true tumours. Some of them represent disturbances of eruption or other developmental malformations and such cysts are often demonstrably connected with malformed or malerupted teeth or they may contain supernumerary teeth or denticles. Others, like the simple dental cysts attached to the roots of dead or diseased teeth, are related to root granulomas in which plentiful epithelial tissue is often present associated with the inflamed granulation tissue. This epithelium is derived from the paradental residues around the roots and epithelium lined root-cysts clearly arise from it. The so called radicular odontomes—abnormal masses of dentine and cementum attached to the roots of teeth—are related to the root cysts and granulomas. As Bland Sutton said: "Many radicular odontomes are probably due to inflammatory changes affecting the roots of incompletely developed teeth." Cysts and root granulomas will not be considered further here.

ADAMANTINOMA OR AMELOBLASTOMA

The tumours of the jaws designated by these names are lowly malignant slowly growing epithelial tumours of rather characteristic microscopical structure which closely resembles that of the developing enamel organ but which do not form enamel. Good accounts include those of Simmons (1928), Robinson (1937), Ringertz (1938) and Thoma and Goldman (1946), and the following personally studied cases are illustrative of the group.

Case I—A man aged 43 complained of steady enlargement of the right half of the mandible for 2 years commencing near the first molar teeth. Examination showed great enlargement and expansion of the bone by a tumour 8 centimetres in diameter extending from near the angle to within 2 centimetres of the symphysis externally forming a smooth rounded swelling internally a lobulated mass with impending ulceration of the mucous membrane. Excision of the right half of the mandible along with the involved mucous membrane was performed with good recovery. Examination of the tumour verified its extent and showed firm whitish tumour tissue containing many small cysts. Microscopically this showed masses of epithelial growth partly resembling basal-cell carcinoma of the skin partly resembling enamel organ epithelium and both solid and cystic (Figs 130 and 131).

Case II—Early in 1929 a woman aged 22 complained of swelling of the left side of the mandible for the previous 18 months following tooth extractions. Operation disclosed a polycystic dental cyst which was curetted out. The swelling reappeared during 1930 and increased until June 1931 when operation disclosed polycystic growth which was curetted out and radium inserted. Microscopical examination showed cystic adamantinoma. Deep X ray therapy was applied during the next 3 years but the tumour slowly recurred. In August 1935 conservative operative removal of the affected area of bone was performed and microscopical examination again showed cystic adamantinoma. Further slow recurrence took place and was again treated by local removal this time with success. The patient remained free of the disease in 1943.

Case III—In 1932 a woman aged 29 noticed a swelling diagnosed dental cyst near the left angle of the mandible. This was removed surgically in 1934. At the end of 1938 a recurrent mass of growth was removed. Microscopical examination showed

cystic adamantinoma The tumour rapidly recurred, and in March 1940 it presented as a large lobulated mass projecting into the mouth and extending up into the temporal fossa and down into the neck About 60 grammes of tumour tissue were removed by curettage, this again showed cystic adamantinoma (Fig 132) The patient died in 1941 from extensive recurrence and supervening infection



FIG 130(a) and (b) —Case I Adamantinoma (a) shows solid tumour clumps resembling those of basal cell growths of the skin and containing small squamous cell foci and (b) shows cystic change in stellate reticulum ($\times 50$)

Case IV —A man aged 49 complained of slight swelling of the molar region of the right side of the mandible for 18 months past previous to which he had pulled out a loose tooth the socket of which then failed to heal Operation disclosed a loculated cyst full of granulation tissue which was curetted out Microscopical examination showed cystic adamantinoma Radium treatment was instituted

Case V —Necropsy on a man aged 67 who had complained of enlargement of the mandible for 2 years showed an extensive solid growth replacing the left half of the bone and ulcerating into the floor of the mouth but without metastases Microscopical

are present. These tissues are usually disorderly in arrangement and do not form properly developed teeth, though teeth may be associated with or incorporated in them.

- (d) *Epithelium lined cysts* in the jaws are formed in several different ways and of course are not true tumours. Some of them represent disturbances of eruption or other developmental malformations and such cysts are often demonstrably connected with malformed or malerupted teeth or they may contain supernumerary teeth or denticles. Others, like the simple dental cysts attached to the roots of dead or diseased teeth are related to root granulomas, in which plentiful epithelial tissue is often present associated with the inflamed granulation tissue. This epithelium is derived from the paradental residues around the roots, and epithelium lined root cysts clearly arise from it. The so called radicular odontomes—abnormal masses of dentine and cementum attached to the roots of teeth—are related to the root cysts and granulomas. As Bland Sutton said: "Many radicular odontomes are probably due to inflammatory changes affecting the roots of incompletely developed teeth." Cysts and root granulomas will not be considered further here.

ADAMANTINOMA OR AMELOBLASTOMA

The tumours of the jaws designated by these names are lowly malignant slowly growing epithelial tumours of rather characteristic microscopical structure which closely resembles that of the developing enamel organ but which do not form enamel. Good accounts include those of Simmons (1928), Robinson (1937), Ringertz (1938) and Thoma and Goldman (1946) and the following personally studied cases are illustrative of the group.

Case I—A man aged 43 complained of steady enlargement of the right half of the mandible for 2 years commencing near the first molar teeth. Examination showed great enlargement and expansion of the bone by a tumour 8 centimetres in diameter extending from near the angle to within 2 centimetres of the symphysis externally forming a smooth rounded swelling internally a lobulated mass with impending ulceration of the mucous membrane. Excision of the right half of the mandible along with the involved mucous membrane was performed with good recovery. Examination of the tumour verified its extent and showed firm whitish tumour tissue containing many small cysts. Microscopically this showed masses of epithelial growth partly resembling basal-cell carcinoma of the skin partly resembling enamel organ epithelium and both solid and cystic (Figs 130 and 131).

Case II—Early in 1929 a woman aged 22 complained of swelling of the left side of the mandible for the previous 18 months following tooth extractions. Operation disclosed a polycystic dental cyst which was curetted out. The swelling reappeared during 1930 and increased until June 1931 when operation disclosed polycystic growth which was curetted out and radium inserted. Microscopical examination showed cystic adamantinoma. Deep X ray therapy was applied during the next 3 years but the tumour slowly recurred. In August 1935 conservative operative removal of the affected area of bone was performed and microscopical examination again showed cystic adamantinoma. Further slow recurrence took place and was again treated by local removal this time with success: the patient remained free of the disease in 1943.

Case III—In 1932 a woman aged 29 noticed a swelling diagnosed dental cyst near the left angle of the mandible. This was removed surgically in 1934. At the end of 1938 a recurrent mass of growth was removed. microscopical examination showed

(2) Structure

Typically "adamantinomatous" epithelium, depicted in Figs 130-132, consists of well defined clumps with rounded or angulated contours, the marginal cells of which are of tall columnar form with their nuclei away from their bases, and the central cells of which form an open meshwork with many intercellular spaces closely resembling the stellate reticulum of the developing enamel organ. Accumulation of fluid in the intercellular spaces in the epithelium frequently produces small or large cysts, which give a honeycombed or pseudo glandular appearance.



FIG 132—Case III Typical though elongated adamantinoma clumps showing the internal (i.e. non basal) position of the nuclei of the marginal cells ($\times 80$)

Other parts of the tumours may show little or no stellate reticulum, and the structure may closely resemble that of basal cell carcinoma of the skin, especially of the cystic type (Fig 130A). Epidermoid characters also may be present, including spinous cells, small cornified foci, or well formed squamous cell pearls. If epidermoid structure is prominent, distinction from epidermoid carcinoma of the jaw is scarcely possible (see Case V). All structural variants may be found in one tumour. Mitotic figures in the tumour cells are few. Old areas of growth often show gross cystic changes, haemorrhage or patchy calcification. Unerupted teeth or fragments of bone are sometimes found incorporated in the tumours.

(3) Growth and metastasis

Though usually of slow growth the tumours distend, invade and destroy the surrounding bone, and, unless wide excision is carried out, post operative recurrence is frequent. Attempts to distinguish 'benign' and 'malignant'

examination showed carcinoma partly of cornifying squamous type but with areas showing stellate reticular structure in the epithelium. The tumour was provisionally called adamantinoma but it could equally well have been called epidermoid carcinoma with adamantinoma like structure.

Case VI (Case XI of Chapter 18)—A woman aged 46 with enlarging tumour of left maxillary antrum for 4 years

(1) Age, sex, race and site incidence

In a review of 379 recorded cases, Robinson found that the average age when the tumours were first noticed was 30 years and that 70 per cent of them appeared



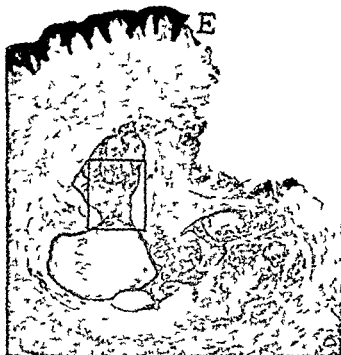
FIG 131—*Case I* Typical adamantinoma clumps ($\times 100$)

between the ages of 10 and 35 years. They may appear in childhood or infancy, Euler saw one in a child aged 13 months and referred to another proven case at 6 months. They rarely appear over the age of 50 years. Many of them are of slow growth and long duration even as long as 40 or 50 years but more rapidly growing tumours (like my Case I) are not unusual. Untreated tumours may attain huge sizes, even as much as 1 500 grammes.

The sexes are about equally affected. 54 per cent of the cases reviewed by Robinson were females. The disease occurs in Negroes Chinese and Indians. Adamantinomas occur more frequently in the lower than in the upper jaw—in 84 per cent of the cases reviewed by Robinson and in the same percentage of Geschickter's cases. This difference may however be partly fictitious since some at least of the maxillary adamantinomas escape recognition as such and are classed as adenoid or basal-celled growths of the antrum or nasal cavity (see Chapter 18).

supported by the following very early case of subgingival epidermoid carcinoma

Case VII—A woman aged 60 had recently noticed a small firm well defined nodule on her lower molar gum margin beneath her dental plate. This measured about 4 millimetres in diameter and was clothed by intact healthy mucosa. Microscopical examination after excision (Figs 133 and 134) showed it to be a circumscribed epidermoid carcinoma with plentiful cornification and some small cysts in the epithelial masses



FIGS 133 and 134—*Case VII* Early squamous-cell growth of subgingival epithelial residues
E = epithelium of gum ($\times 15$ and 120)

adamantinomas are futile, they are all malignant in that they are locally invasive and prone to recur. Metastasis to the cervical lymph glands or lungs is infrequent, but has occurred in a few cases e.g. in those of Ewing, Simmons (Cases 2 and 7) and Vorzimer and Perla. Vorzimer and Perla's case showed unique intrabronchial metastasis evidently due to inhalation of tumour fragments from the advanced maxillary adamantinoma which had invaded the nasal cavity and pharynx.

(4) Comment on histogenesis

The frequently unmistakable resemblance of adamantinoma to enamel organ epithelium points to this tissue as the origin of the growth. The failure of the tumour to form enamel though perplexing to those who accept the names adamantinoma and ameloblastoma at their face value, accords with the developmental history of the tooth germ epithelium. The only part of this destined to form enamel is the *internal enamel epithelium* or layer of ameloblasts. external epithelium and stellate reticulum form no enamel either in normal development or in tumours. To call these tumours by either of the prevalent names is therefore erroneous. It would be better to call them carcinomas of the tooth germ residues.

It is relevant to mention here the so called adamantinomas of extra oral sites the pituitary region and the tibia. The dental lamina arises as an outgrowth of the embryonic oral ectoderm and leaves epithelial residues around its special derivatives the teeth. so also Rathke's pouch arises as an outgrowth of the same oral ectoderm and leaves epithelial residues around its special derivatives the epithelial parts of the pituitary gland. It is then not difficult to understand why these two groups of indifferent epithelial residues should give origin to tumours of similar structure and with a similar incidence at relatively early ages. Further, the adamantinomas of the pituitary region clearly have no histogenetic relationship to any enamel forming epithelium—a further reason for recognizing this name as a misnomer. The so called adamantinomas of the tibia (Chapter 14) are bone invading epidermal carcinomas parts of which sometimes show some structural resemblance to the oral and pituitary adamantinomas but of course occasional resemblance is not identity. Even ordinary squamous cell carcinoma of the skin occasionally resembles adamantinoma (Fig 93).

INTRA ALVEOLAR EPIDERMOID CARCINOMA

Rarely a squamous cell carcinoma of ordinary structure and behaviour arises in the substance of the jaw. widely invades and destroys the bone and may ulcerate secondarily into the mouth. I have performed necropsies on two such cases, one in a woman aged 63 years and the other in a woman aged 75 both with metastases in the cervical lymph glands. Case V above might also be placed in this group. The number of recorded tumours of this kind is too few for analysis of their properties but most of them have appeared in elderly people and have shown a degree of malignancy like that of oral epidermoid carcinoma in general. In spite of tumours of borderline structure, like Case V the group on the whole is distinct from the adamantinomas suggesting a different origin doubtless the squamous celled residues of the dental lamina (Fig 129). This origin is

fully formed dentine and enamel related to each other as in normal tooth development but with disordered arrangement, including, as in Pritchard's specimen, reversed position of dentine and enamel

Horbst's case, a girl of 9 years, provided a good example of the rare soft odontomes, containing young tooth germs with embryonic connective tissue clothed by epithelium, but without fully formed dentine or enamel. Such odontomes with immature tissues have sometimes been called "adamantinomas", but as Euler insisted, the two can and should be distinguished.

Mummery and Pitts reported a unique odontome removed from the incisor region of an infant, in addition to dental tissues, this growth contained melanotic epithelial tissue. Its benign character was attested both by its encapsulation and the fact that there was no recurrence 4 years after its removal. Although described as an "epithelial odontome" and included by Robinson in his review of ameloblastomas, this tumour must be classed with the odontomes proper.

TUMOURS OF DENTAL TISSUES IN ANIMALS

In most cases, dental "tumours" in animals are not true neoplasms but cystic malformations or odontomes. These have been seen in great number and variety in most species of domesticated animals and in many wild species also. Colyer has fully described and depicted many examples. Bullock and Curtis observed odontomes in rats, and Zegarelli in mice.

Adamantinomas comparable with the human tumours have rarely been reported from animals. Zegarelli described as "adamantoblastoma" 103 solid or cystic growths in the jaws of mice, some of which appear clearly to have been true tumours mainly of squamous cell type, while others were non-neoplastic odontomes. Nieberle and Cohrs stated that adamantinomas occur in the ox and cat, and Ratchliffe that he had seen one example in a rat, but no details are given. The tumour described by Orr as "adamantinoma" in a rabbit was a squamous cell growth associated with cysts lined by ordinary squamous stratified epithelium.

REFERENCES

- Bland Sutton J (1922) *Tumours Innocent and Malignant* Chapter 22 London
 Bullock F D and Curtis M R (1930) *J Cancer Res* 14 1
 COLYER, F (1936) *Variations and Diseases of the Teeth in Animals* Chapter 23 London
 (Many odontomes beautifully illustrated)
 EULER H (1933) Vom Zahnsystem ausgehende Geschwulste des frühesten Kindesalters
Dtsch Zahn Hschr 36 206 and 228 (A careful and interesting study of dental tumours
 in infants)
 Ewing J (1928) *Neoplastic Diseases* p 758 Philadelphia
 Geschickter C F (1935) *Amer J Cancer* 24 90
 Horbst L (1934) *Arch Ohr usw Heilk* 138 30
 Huxley J S and De Beer G R (1934) *Elements of Experimental Embryology* pp 487 and 498
 Cambridge
 MUMMERY, J H (1919) *The Microscopic Anatomy of the Teeth* pp 262 and 322 London
 (A good account of tooth structure and development)
 Mummery J H and Pitts A T (1926) *Brit Dental J* 47 121
 Nieberle K and Cohrs P (1931) *Lehrbuch der Speziellen Path Anat der Haustiere* p 236
 Jena

The tumour diagnosed by Orr (1936) as 'adamantinoma' in a rabbit was a cystic squamous cell growth

ODONTOMES

It is questionable whether the odontomes are neoplasms. Many of them are known to have been present since infancy or childhood, and to have enlarged only *pari passu* with the growth of the rest of the dental tissues or as the result of secondary infection and inflammation. In these respects they behave rather like malformations than like true tumours. I propose therefore to devote little space to them but to refer the reader to the naked eye descriptions of Bland-Sutton (who gave earlier references), and to the detailed histological studies of Rywkind, Pritchard, Euler, Horbst, and Thoma and Goldman. These show clearly the disorderly arrangement of the tissues in odontomes, the presence of tissues at all stages of formation, the dependence of dentine formation on the presence of epithelium, and the frequent reversal of position of these two tissues, enamel and enamel organ epithelium often being found centrally situated within masses of dentine.

The following is an example of an old fully mature quiescent odontome.

Case VIII—A man aged 47 years had had a swelling of his maxilla for many years, this had remained unchanged until an adjacent tooth had been extracted, since when the mass had been tender and a small discharging sinus had persisted. At operation a well defined irregularly rounded mass 2 centimetres in diameter, situated in the right maxilla in the lateral incisor and canine region, was removed. Serial sections after decalcification showed it to be a conglomeration of denticles or tooth-like masses consisting mainly of dentine clothed here and there by a layer of enamel of very irregular distribution and thickness. Lying between the better formed denticles there were also smaller irregular pieces of dentine, many of which showed vacuolation and spherical calcified bodies. The soft tissue intervening between the tooth tissues was largely inflamed granulation tissue in which however there were scattered groups of epithelial cells.

Pritchard summarized his well illustrated account of an odontome in a boy of 7 years as follows. This tumour started at a very early age in the backward growth of the tooth band distal to the first molar, in that part of it destined for the formation of the second and third molar teeth. It consisted at first of branching columns of columnar epithelium which burrowed in the embryonic connective tissue in the interior of the mandible. As it grew it determined the formation of dentine which subsequently calcified in contact with it, enamel calcifying approximately simultaneously. As the dentine formed neighbouring masses coalesced or tended to do so, to surround or enfold columns of enamel. The connective tissue more remote from the growing epithelium tended to reach maturity and form fibrous tissue which in the end would have become the fibrous capsule of the mass. At or after this stage cementum deposition would have become possible. As in the case of a tooth when the enamel organ and Hertwig's sheath have completed their primary function of shaping the tooth, and in the former instance also of forming enamel, epithelial growth stops, so in the case of such an odontome would growth cease at the end of formation and calcification.

Rywkind's excellent study of an odontome in a girl of 8 years showed all stages in the formation of dental tissues from early tooth germ tissue up to

CHAPTER 17

EPITHELIAL TUMOURS OF THE SALIVARY GLANDS

MANY of the earlier writers on salivary tumours sharply distinguished the rare adenomas and carcinomas from the much larger group of so called "mixed" tumours. This distinction, we may now recognize, was an artificial one, for, as will be shown the "mixed tumours" are adenomas and lowly malignant adenocarcinomas, with a wide range of structure and behaviour, and they merge insensibly with the simple adenomas on the one hand and with the frankly malignant anaplastic carcinomas on the other. Hence, while it is convenient for descriptive purposes to continue to use these names it is essential to understand that they denote, not distinct classes of tumours but merely variants of a single histogenetic group. With this clearly in mind and adding the distinctive group of rare adeno-lymphomas we shall discuss the salivary epithelial tumours under the following main heads

- (a) Simple adenomas
- (b) Pleomorphic adenomas and adenocarcinomas (so called 'mixed' tumours)
- (c) Anaplastic carcinomas
- (d) Adeno lymphomas

SIMPLE SALIVARY ADENOMAS

A few salivary tumours are so uniform in structure and composed of epithelial tissue so unmistakably like that of the salivary glands, that their simple epithelial character has always been admitted, and accordingly they have been separated from the supposedly "mixed" tumours under the quite correct caption of "adenomas".

However, the view already expressed that this separation is artificial, rests on the following grounds. (a) Areas of simple adenomatous tissue resembling that of the simple adenomas are to be found in the "mixed" tumours. (b) Otherwise typical salivary adenomas may show in minor degree some of the structural characters of the "mixed" tumours thus Ewing said 'several authors have described transitions to myxo chondro carcinoma', Fry concluded that on structural grounds no sharp line can be drawn between adenomas and mixed tumours, and Harvey *et al* in their Fig 16 depicted a densely encapsulated tumour of pure adenomatous type with a mucoid stroma. (c) If the supposedly "mixed" tumours are, as will be shown not mixed but are purely epithelial growths arising from salivary glandular tissue then clearly there can be no sharp distinction between these and the simple adenomas for they are of identical origin. The adenomas are then only a variant of the whole group, namely the most slowly growing and innocuous variety with a uniformly differentiated structure.

Typical examples of adenomas were described by Schutz, Steinhardt, and Škorpil, and Eggers classified 2 of his 7 palatal tumours as adenomas. Schutz

- ORR J W (1936) *J Path Bact* 42 703
- PRITCHARD G B (1932) The origin and growth of a composite odontome *Proc Roy Soc Med*, 26 472 (A valuable well illustrated study)
- RATCHLIFE H L (1940) *Amer J Path* 16 237
- RINGERTZ, N (1938) *Reference* Chapter 18
- ROBINSON H B G (1937) *Arch Path* 23 664
- ROBINSON H B G (1937) Ameloblastoma A survey of 379 cases from the literature, *Arch Path* 23 831
- RYWAKIND, A W (1930) Zur Pathologie der Odontome, *Virchows Arch*, 277 228 (An excellent account with beautiful illustrations)
- SIMMONS C C (1928) *Ann Surg* 88 693
- THOMAS, K H and GOLDMAN, H M (1946) Odontogenic tumors *Amer J Path*, 22 433 (Good illustrations show well the range of structure in the tumours and odontomes)
- VORZIMER J and PERLA D (1932) *Amer J Path* 8 445
- ZEGARELLI, E V (1944) Adamantoblastomas in the Slye stock of mice *Amer J Path* 20 23 (A well illustrated account of odontomes and dental epithelial tumours)

of cells already in an advanced state of differentiation" Ewing (1940), while appearing at first to support the epithelial salivary origin of the tumours, then supposed that, 'No single source of the mixed tumors meets all the requirements', that some of the tumours "probably arise from misplaced, and occasionally, embryonal portions of gland tissue", and that "branchial remnants may possibly be connected with this group" So also, Kaufmann (1929) after expressing adherence to "the epithelial theory", qualified this by adding 'that an endothelial derivation is possible exceptionally' Ahlborn in his monograph (1935) gives much useful information about salivary tumours, but vacillates over their histogenesis and speaks of "chondroma", "fibro myxo epithelioma" etc.

Thus in the works of recent and authoritative writers, we find views expressed which show that none of the old notions is quite extinct—Cohnheim's embryonic cell rests, branchial enclavement, endothelial origin, are all represented

Many of those workers who have argued for the essentially epithelial salivary origin of the tumours, have nevertheless accepted without question the prevalent belief that they contain "cartilage", and have devised various explanations of the origin of this cartilage" Usually they have then continued to speak of "mixed" tumours explaining the "cartilage" as a product of metaplasia in the stroma (e.g. Muir, 1941) or by concluding that true cartilage may arise by direct transformation of the epithelium itself Thus according to Ewing 'the derivation of mucous tissue and cartilage from gland epithelium has been satisfactorily proved

In what follows I shall present briefly the evidence which fully convinces me that, (a) these tumours are not "mixed" but arise from and consist of salivary epithelial tissue only, (b) with very rare exceptions, they contain no mucous connective tissue and no cartilage, and (c) in those rare tumours in which cartilage (or bone) is present this is quite different from the supposed 'cartilage' so common in the tumours and has clearly arisen by metaplasia in the connective tissue stroma just as may occasionally happen in many other kinds of tumours I must say also that, granted some justification for the conflicting views of the earlier explorers of this field, I find myself unable to comprehend how any modern histopathologist after studying the structure of these growths with reasonable care, could possibly come to any other conclusions than the foregoing

Some workers, though satisfied of the simple epithelial nature of the tumours have retained the term 'mixed' as appropriately denoting the variety of structure in the growths Because of the erroneous connotation of the term, however I prefer to discard it in favour of the purely descriptive adjective "pleomorphic

(2) Age incidence

These tumours arise at all ages from early childhood onwards but the greatest number make their appearance in the third and fourth decades (Wilson and Willis, McFarland) More than one half of the tumours appear during these two decades, between which they are distributed about equally Two thirds of the tumours begin before the age of 40 and nearly seven eighths of them before the age of 50 Their first appearance in old people is quite rare They are not unusual in childhood and early adolescence, e.g. at 15 (Harvey *et al*), 10 (Fry), and 9 years (Chevassu, Zymbal), and occasionally they are

insisted that a diagnosis of adenoma can only be made after thorough examination of all parts of a growth since a tumour the bulk of which is adenomatous may show small areas of 'mixed' structure. The pure adenomas are slowly growing encapsulated tumours composed of lobular masses of epithelial tissue which may be partly of acinar structure but may be largely solid and devoid of lumina. Acinar cavities in adenomas may contain mucoid secretion.

PLEOMORPHIC SALIVARY ADENOMAS AND ADENOCARCINOMAS (SO CALLED MIXED TUMOURS)

(1) The confusion of ideas and names

About nine tenths of all salivary tumours fall in this group, commonly designated mixed tumours. The term mixed a misnomer when applied to the growths themselves is an apt enough description of the many conflicting and ill founded views which have been expressed regarding their histogenesis. In 1909 Fick was able to say 'On the interpretation of mixed tumours scarcely two authors agree on all points' and while an increasing number of competent pathologists (e.g. Fick, Krompecher, Bottner, Fry, Patev, Zymbal, Harvey *et al.*) have become convinced of the pure epithelial nature of these tumours we are still far from unanimity.

It would serve no useful purpose to review in detail the bewildering welter of hypotheses regarding the mixed tumours for most of them lack any real basis and they have been adequately outlined by Wood, Krompecher, Bottner, Chevassu, Ahlborn and others. Suffice it to say that these tumours have been called sarcoma, endothelioma, mesothelioma, chondroma, cylindroma, adeno chondroma, chondro carcinoma, branchioma, enclavoma, progonoma, teratoma and teratoblastoma as well as such hyphenated monstrosities as fibro myxo endothelioma, adeno myxo chondro sarcoma and chondro myxo haemangio-endothelio sarcoma. This chaos of names (surely a warning for would be nomenclators) is indication enough of the diversity of ill founded views which have been held regarding the nature of these tumours.

These names and views would be only of antiquarian interest did not some quite recent authorities still cling to part or whole of some of the erroneous notions implied in them. Thus McFarland (1926) insists that the tumours do not arise from salivary tissue and thinks that enclavement of embryonic cells affords the best explanation of their origin. He says 'Mixed tumors are individual entities having no relation to the normal structures in which they occur but from which they do not arise. They have nothing to do with other kinds of tumors and should be called mixed tumors' and nothing else regardless of their histology. McFarland expressed similar views in his *Surgical Pathology* (1924) and did not indicate any alteration of them in his recently published paper (1942). Kux (1931) and Hempleman and Womack (1942) upheld the view that they are 'truly mixed tumors' related in their origin to embryonic alteration in tissue relationships. MacCallum (1940) thought 'most acceptable and credible' the view that these tumours represent the teratoma derived from the isolation

The relative frequencies of tumours in these various sites may be judged from the accompanying Table, which includes only tumours of clearly specified situations

TABLE

	Parotid	Submaxillary	Sublingual	Palate	Lips and other sites	Total
Patey - - - -	38	6	—	5	5	54
Zymbal - - - -	55	2	—	—	1	58
Harvey <i>et al</i> - - - -	230	21	2	6	9	268
Willis - - - -	35	6	1	5	1	48
Totals - - - -	358	35	3	16	16	428
Percentages - - - -	83	8	1	4	4	100

McFarland's large series (1942) is not given in this table because he considered only tumours of the three major glands—these comprised 380 from the parotid 12 from the submaxillary and 2 from the sublingual gland, though McFarland admitted that the proportion of submaxillary tumours in his series might be under-estimated. Submaxillary tumours are specially considered by Chevassu, and by Dockerty and Mayo, and palatal tumours by Eggers and Aunoy, Davis and Stobie.

The Table shows that, approximately, for every 100 parotid tumours, there are likely to be seen about 10 submaxillary tumours, 10 tumours of the minor salivary glands (of which about half will be palatal), and only one sublingual tumour. These estimates agree almost exactly with those of Bohme (cited by Wood), who found parotid tumours to be ten times as frequent as submaxillary tumours and sublingual tumours to comprise one per cent of the total. These differences are too great to be accounted for entirely by the relative bulks of the three glands, the approximate average weights of which are parotid 25 grammes, submaxillary 8 grammes, and sublingual 3 grammes. We must also postulate differences in the susceptibility of the respective tissues to neoplasia. Since the parotid acini consist almost entirely of serous or albuminous cells and the submaxillary gland contains a higher proportion of these than the sublingual gland, it may be that the serous or albuminous type of cell is more prone to neoplasia than the mucous type. We shall see later whether or not histogenetic studies support this supposition.

A final point regarding the situation of the tumours with respect to the affected glands requires comment. While in most cases the tumour quite clearly lies within the gland, several workers have observed tumours contiguous with but separate from the parotid or submaxillary glands and this fact has been used as an argument in favour of an origin extrinsic to salivary tissue, e.g. from branchial remains. The unsoundness of this argument will be obvious to anyone familiar with the anatomy of the salivary glands outlying lobules or tubules of which especially of the parotid are often to be found in the surrounding tissues, or included within neighbouring lymph glands (Nicholson).

seen in infants e.g. in Schilling's case a parotid tumour removed from a man of 41 years had been present since the age of one year and in one of Wood's cases a parotid tumour was noticed soon after birth and was removed at the age of seven months. Of 380 cases collected by McFarland 8 occurred in the first decade of life. In my own series the lowest recorded age was 14 years, while another tumour subsequently fatal from metastases at the age of 29 had first appeared at the age of 16. McFarland (1936) shows that the age of appearance of the tumours has no bearing on their degree of innocence or malignancy. The ages at the time of first operation are on an average about 6 years later than the ages when the tumours first appeared. In my own series the ages at operation were as follow

Decade	-	-	1	2	3	4	5	6	7	8	
No. of cases	-	0	2	8	12	6	5	6	0	= 39 cases	

Average age at time of operation 38 years

(3) Sex incidence

Although there is but little difference between the sexes in their liability to salivary tumours many of the recorded series show a predominance of females. Thus Bottner's 25 cases comprised 15 females and 10 males. Fry's 25 cases 14 females and 11 males, McFarland's 396 cases 212 females and 184 males and in my own series of 50 cases of known sex, there were 34 females and 16 males. Some series, however, have not shown an excess of females e.g. Chevassu's study of 57 tumours of the submaxillary gland comprised 30 males and 27 females, and of the 56 mixed salivary tumours of Wilson and Willis's series 30 were in males and 26 in females.

(4) Race and species incidence

There are no reliable comparative statistics. That all the main European peoples are liable to salivary tumours is shown by the plentiful cases in English, French, German, Italian and Russian reports. American records contain in addition references to salivary tumours in negroes and they occur also in the Chinese (Balme, Yen, Davis) and Hindus (Street).

Harvey and co authors briefly mention five mixed salivary tumours in dogs.

(5) Site

The parotid is much more frequently affected than the other salivary glands but similar tumours arise from salivary glandular tissue wherever situated not only from the three pairs of large glands but also from the small glands which are widely distributed around the oral cavity in the lips, cheeks, palate and floor of the mouth.

(7) The structure of the tumour parenchyma

By far the best account of the microscopical structure of salivary tumours is that of Zymbal of Leningrad (1933), whose beautifully illustrated paper is a model of scientific clarity. Anyone who can read Zymbal's paper and still doubt the simple epithelial nature and origin of the so called "mixed" tumours is pathologically incorrigible. Other commendable accounts are those of Patey (1931), Fry (1928), and Harvey and co authors (1938). The following outline, which is based on my own series of specimens, accords with the descriptions of these workers.

The structure of the tumours is very variable, in some tumours many or all of the possible variations of structure may be found in close juxtaposition with all gradations between them, in other tumours one or another structural variant predominates. The following types of structure may be described in turn

- (a) Nearly normal looking salivary tissues
- (b) Atypical glandular tissue
- (c) Atypical glandular tissue with marginal epithelial sprouting
- (d) Solid epithelial formations
- (e) Epithelial formations with cystic spaces
- (f) Cornifying stratified epithelial structures
- (g) Epithelial filaments and networks in a mucinous matrix
- (h) The so-called 'cartilage like' tissue
- (i) Areas with frankly carcinomatous characters

(a) *Nearly normal looking salivary tissues*

Many of the tumours contain acinar and duct like structures which, divorced from the atypical tissues with which they are mingled, closely resemble the acini and ducts of normal salivary tissue. The most typical acini are to be seen in regions where, as will be described later, there is a direct transition of salivary tissue into tumour. In these situations as Fry has pointed out and I can confirm (see Figs 142-144), typical salivary acini still with zymogen or secretory granules in the cells constitute part of the growth. Although glandular acini deeper in the growths show no typical granules in the cells, they are often unmistakably like salivary acini in other respects, both as regards their general arrangement with respect to duct like structures and their cytology. Instead of containing darkly stained secretion granules, the cytoplasm usually appears finely foamy or vacuolated as though secretory material had been dissolved out. As regards duct like structures in the tumours, Fry, Harvey *et al* and others have pointed out the frequent presence of elongated or branching tubules lined by a double layer of epithelial cells resembling or identical with those of normal salivary ducts. From my own specimens I can confirm this to be a very common feature. From the findings in Case I, above, and Case III, to be described, as well as from the general relationship of these tubules to lobular clusters of tumour acini in some of the growths, I strongly suspect that some at least of these tubules are not merely duct-like structures formed as the tumour grows, but actually salivary ducts which have participated in the neoplastic change along with their attached lobules of acini.

(6) Relation to antecedent disease

With few exceptions, the subjects of salivary tumours give no history of antecedent disease of the glands and there is no positive evidence that mumps suppurative parotitis, salivary calculi or trauma predispose to tumour formation. However information on these points is rarely recorded in hospital histories, and there is room for a deliberate inquiry regarding them from patients with salivary tumours



FIG 135—*Case 1* A fibrotic area of parotid tissue on the outskirts of the tumour it was impossible to be sure whether this area was an altered parotid lobule or part of the tumour it was probably both i.e. an area of transition from gland to tumour ($\times 72$)

In many cases pieces of salivary gland attached to excised tumours show no histological abnormalities. In a few cases however chronic inflammation, fibrosis and parenchymatous atrophy are present and while these changes may often be attributable to duct obstruction and other secondary results of the tumours themselves cases such as the following suggest that tumour formation may supervene on previous disease

Case 1—A man aged 69 years had noticed a lump in front of his ear for several months. A somewhat irregular mass about 3 centimetres in main diameter and not sharply encapsulated was excised. Microscopically this consisted partly of small masses of rather cellular epithelial growth surrounded by much dense fibrous tissue and partly of many lobules of altered parotid tissue which showed an extreme degree of fibrosis accompanied by atrophy of acini and ducts and moderate infiltration by round cells. In several places transitions were apparent (Fig 135). Thick masses of dense hyaline fibrous tissue up to 6 millimetres wide and devoid of both parotid and tumour tissue were interspersed through the tumour and some calcification was present in this in places

acinar and duct-like structures already described, but without lumina (Figs 137, 145) Growth and confluence of these produce large masses of many shapes

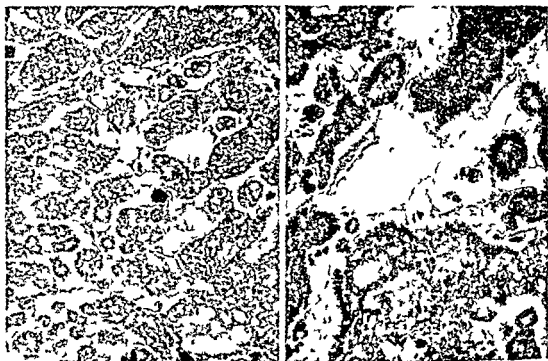


FIG 137—Solid epithelial clumps and columns with acinar cavities in places and intervening mucoid matrix in a parotid tumour from a woman of 50 years ($\times 72$)

and sizes Epithelial masses may contain solid spherules of eosinophilic secretory material (Fig 138)



FIG 138—Solid epithelial mass containing a spherule of eosinophil secretion ($\times 450$)

(e) *Epithelial masses with cystic spaces*

In large epithelial masses rounded or irregular spaces may appear chiefly by the collection of secretory products of the cells Sometimes the secretory

(b) Atypical glandular tissue

This is seen in a great variety of forms. These may be acinar or ductular in type, they may be cystic or finely papillary. They may contain mucoid or hyaline material or no visible secretion and they frequently assume convoluted and anastomosing patterns closely resembling those of the intra canalicular structure in mammary fibro adenomas (illustrations by Harvey *et al*). Predominance of mucus secreting goblet celled epithelium is sometimes seen as in the cases of Schilling (1921) Lepp (1939), De and Tribedi (1939). However this is not such



FIG. 136—Glandular tissue with epithelial sprouts passing into mucinous matrix simulating cartilage from a submaxillary tumour in a woman of 39 years ($\times 72$)

a wide departure from normal salivary structure as some writers have made out since mucus secreting cells are present not only in the acini of the mixed glands but also in all salivary ducts

(c) Atypical glandular tissue with marginal epithelial sprouting

A very frequent finding in these tumours particularly well described and depicted by Zymbal, and illustrated in Fig. 136 is the outgrowth of thin strands of epithelium from glandular formations. Sprouts or sprays of cells spread out from these into a surrounding lake of mucinous material where they become very tenuous and the cells often detached. This fraying out of epithelium is a common mode of development of the so called "mucoid tissue" and "cartilage" to be described later

(d) Solid epithelial formations

These are again of very diverse appearance. Many tumours contain solid clumps or columns of epithelium, identical in the characters of their cells with the

acinar and duct-like structures already described, but without lumina (Figs 137, 145) Growth and confluence of these produce large masses of many shapes

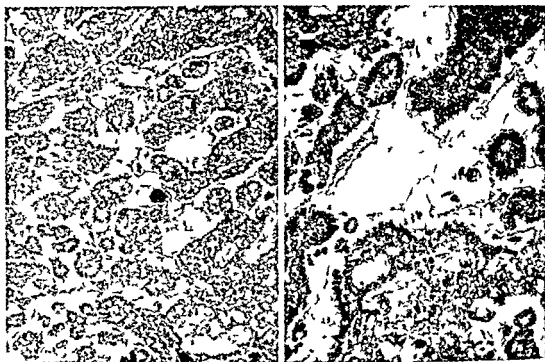


FIG 137—Solid epithelial clumps and columns with acinar cavities in places, and intervening mucoid matrix in a parotid tumour from a woman of 50 years ($\times 72$)

and sizes Epithelial masses may contain solid spherules of eosinophilic secretory material (Fig 138)



FIG 138—Solid epithelial mass containing a spherule of eosinophil secretion ($\times 450$)

(e) *Epithelial masses with cystic spaces*

In large epithelial masses rounded or irregular spaces may appear, chiefly by the collection of secretory products of the cells Sometimes the secretory

spaces assume a characteristic cribriform structure (Fig 139) which closely resembles that seen in mammary tumours or in adenoid cystic tumours of the skin or nasal cavity. These gland like spaces however differ from true acinar and duct lumina in the absence of definite glandular orientation of the epithelial cells around them. Cysts formed by necrosis of tumour tissue are rarely or never seen in the salivary tumours.

(f) *Cornifying stratified epithelial structures*

Quite commonly parts of these growths develop epidermoid characters stratification prickle cells and cornification (Fig 140). This squamous celled

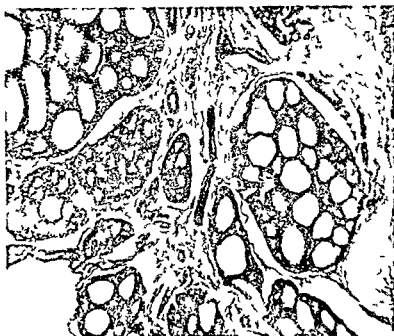


FIG 139.—Cribriform structure in parotid tumour from a man of 25 years ($\times 72$)

metaplasia is comparable with that seen in adenocarcinomas of other glandular organs and it is not surprising that it should occur commonly in tumours of salivary origin since developmentally the salivary glands are but outgrowths of the ectodermal buccal epithelium and indeed the terminal parts of the salivary ducts themselves show stratification. Another type of stratified epithelium sometimes seen in these tumours presents an open meshwork resembling that of the stellate reticulum of adamantinomas (Fig 141) a resemblance again not surprising in view of the close developmental affinities of the original tissues.

(g) *Epithelial filaments and networks in a mucinous matrix*

Under (c) we have already noticed the frequent fraying out of epithelium to form strands in lakes of mucinous material. This change frequently produces more or less extensive areas of fine epithelial filaments or a meshwork suspended in the mucinous matrix. It is this type of structure which has often been called

"myxomatous" —a false name however, since the tissue is not mucoid connective tissue. The epithelial nature of the cells is quite clear, not only from their frequently obvious derivation by sprouting from glandular tissue but also as Zymbal has most clearly shown, by the presence in the cells of plentiful droplets of mucoid secretion. The mucinous matrix in which the cells are suspended is clearly formed by this secretion of the cells themselves. Sometimes at the margin of a tumour,



FIG 140—Cornified cell nests along with some glandular structures in a sublingual tumour from a woman of 39 years ($\times 75$)

direct transformation of normal salivary acini into mucinous epithelial reticulum is apparent (Figs 142-144)

(h) "Cartilage like" areas

I put "cartilage like" in inverted commas deliberately, because I agree with Patey, Zymbal and others that this tissue rarely shows any close resemblance to cartilage. It represents only a further change in the "myxomatous" tissue, in which the epithelial cells have become more widely separated and partly detached from one another in the mucinous matrix (Fig 136)

The peculiar and variable metachromatic staining properties of this matrix do not warrant the conclusions drawn from them by Kux and by Hempleman and Womack. These workers upheld the term "mixed" tumours on the ground that different staining techniques enabled them to distinguish epithelial from mesenchymal mucin to identify both types of mucin in the salivary tumours, and to prove the mesenchymal nature of the myxomatous and cartilaginous areas. These claims cannot be accepted. It is true that the matrix of these areas stains differently from the mucus within epithelial cells and in the lumina of epithelial cavities. This however, is no proof of its mesenchymal origin. gradual

spaces assume a characteristic cribriform structure (Fig 139) which closely resembles that seen in mammary tumours or in adenoid cystic tumours of the skin or nasal cavity. These gland like spaces however differ from true acinar and duct lumina in the absence of definite glandular orientation of the epithelial cells around them. Cysts formed by necrosis of tumour tissue are rarely or never seen in the salivary tumours.

(f) Cornifying stratified epithelial structures

Quite commonly parts of these growths develop epidermoid characters stratification prickly cells and cornification (Fig 140). This squamous celled

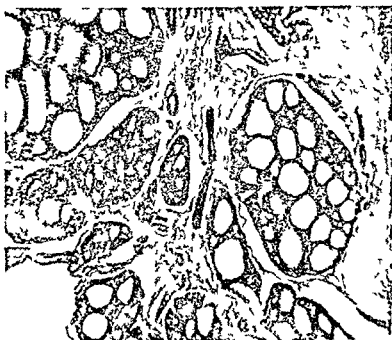


Fig 139 —Cribriform structure in parotid tumour from a man of 25 years (< 72)

metaplasia is comparable with that seen in adenocarcinomas of other glandular organs and it is not surprising that it should occur commonly in tumours of salivary origin since developmentally the salivary glands are but outgrowths of the ectodermal buccal epithelium and indeed the terminal parts of the salivary ducts themselves show stratification. Another type of stratified epithelium sometimes seen in these tumours presents an open meshwork resembling that of the stellate reticulum of adamantinomas (Fig 141) a resemblance again not surprising in view of the close developmental affinities of the original tissues.

(g) Epithelial filaments and networks in a mucinous matrix

Under (c) we have already noticed the frequent fraying out of epithelium to form strands in lakes of mucinous material. This change frequently produces more or less extensive areas of fine epithelial filaments or a meshwork suspended in the mucinous matrix. It is this type of structure which has often been called

for chemical research on the diastase content of salivary tumours and on the chemical changes which may occur in artificial mixtures of salivary diastase and salivary mucus. It may well be that the interaction of both secretions of the tumour cells, probably produced in variable proportions in different tumours, accounts for the peculiar and variable physical and staining properties of the mucinous material. Clearly, then, we cannot draw any deductions as to the origin of this material from its staining properties.



FIG 143—Case II. Islands of darkly stained residual parotid tissue (P) are deeply included in the mucinous growth ($\times 5$)

It may also be added here that scattering of detached epithelial cells in pools of their own secretion and slow changes in the characters of that secretion are not peculiar to salivary tumours but are seen also in mucoid adenocarcinomas (‘colloid cancers’) of the alimentary canal or breast. In these, however, the intra cellular secretion usually appears as a single large droplet of mucus in a signet ring cell, instead of many fine droplets as in the cells of the salivary tumours.

(i) Areas with frankly carcinomatous characters

In tumours with a history of recent rapid growth, or of rapid recurrence or metastasis while parts of the tumour may still show structural characters of the foregoing types much of the growth may consist of more cellular anaplastic tissue rich in mitoses. The cells may be spheroidal, spindle shaped or pleomorphic, like those of the anaplastic salivary carcinomas described below (see Figs 147, 149) and their arrangement may be in compact epithelial clumps or diffuse.

Pleomorphism is a striking feature of this group of tumours. Any or all of the foregoing varieties of structure may occur in one tumour. Obvious gradations

chemical changes certainly take place in long stagnant pools of extravasated secretion. As Fry points out, such changes may be related to deficient nutrition,

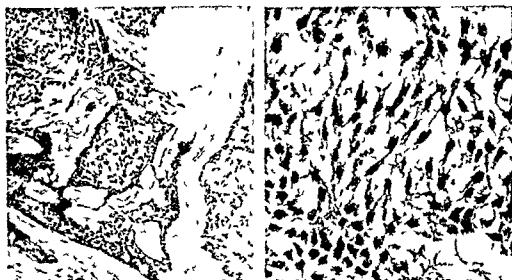


FIG 141 — Adamantinoma like structure with stellate-celled epithelial reticulum in a parotid tumour from a woman of 56 years ($\times 120$ and 400)

since the cells and matrix in the centre of a large mucinous area are remote from blood vessels. Another factor also may operate in producing chemical alteration of the mucinous matrix. This is the probable secretion not only of mucin but

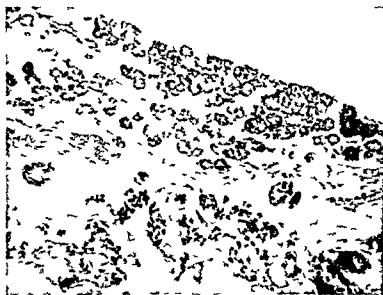


FIG 142 — Margin of a parotid tumour from a woman of 50 years showing direct transformation of parotid acini (above) into mucinous tumour tissue (below) (> 120)

also of ptyalin by the tumour cells and the chemical effects of this carbohydrate-splitting enzyme on the carbohydrate component of the mucin. There is room

the one hand to mucinous or "cartilage-like" tumour tissue on the other. The existence of these zones shows clearly, not only that the tumours are derived from salivary epithelium, but also that they take origin, not from a single minute focus at a single moment of time, but progressively from a considerable field of salivary tissue. Dockerty and Mayo reported 4 examples of submaxillary tumours of multicentric origin.

When tumour genesis is progressing simultaneously at many parts of a considerable area of salivary tissue, an intimate admixture of developing tumour

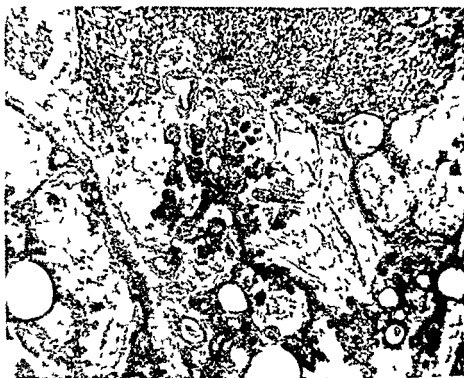


FIG 145—*Case III* Neoplastic ducts and clusters of solid acini interspersed islands of adipose tissue in the stroma ($\times 72$)

and residual salivary tissue may result, with transition zones in many places. A striking instance of this is afforded by the specimen from *Case II*, depicted in Figs 143 and 144.

Case II—A man of 26 years had had a slowly enlarging parotid tumour for 4 years. Seven months prior to his coming for treatment this had been incompletely excised and had recurred. Operation disclosed an irregular lobulated rather ill defined mass of growth 3 centimetres in diameter devoid of a capsule and separable only with difficulty from the surrounding tissues. Not only was the tumour imperfectly demarcated from the surrounding parotid tissue but as Fig 143 shows visible residues of parotid tissue lay here and there through the tumour and there were also many microscopic residues which the low power photograph does not depict. Many regions of direct transition from these residues to tumour tissue were to be seen (Fig 144).

The presence of islands of adipose tissue widely scattered through a tumour is to be explained similarly. An example is shown in Fig 145, from *Case III*.

from one kind of structure to another abound affording clear evidence of the essential identity of the tumour parenchyma in all its variants

Tissue culture from different structural areas of the tumours yields interesting results Zymbal found that explants from areas of well preserved glandular structure, from solid epithelial masses or from the less degenerated reticular areas were capable of growth *in vitro* and survival for periods of up to three weeks, but that explants from advanced reticular or 'cartilage like' areas promptly degenerated *in vitro* The results accord with the suggestion of Fry, Harvey *et al*



FIG 144—Case II A region of direction transformation of parotid acini into mucinous growth ($\times 75$)

and others that the 'myxomatous' and 'cartilaginous' areas are regions of poor nutrition and cell deterioration Zymbal's tissue cultures also showed a variety of forms comparable with those of the tumours—epithelial sheets solid masses networks and isolated cells and further the changes seen in the epithelium of tumour explants resembled those seen in explants of normal salivary tissue

(8) Relationship of tumour parenchyma to salivary tissue mode of origin of the tumours

It has already been mentioned that direct transition, from salivary acini to tumour are sometimes demonstrable This feature noted by Zymbal, Fry, Harvey *et al* is illustrated in Figs 142-144 I have seen it unmistakably in eight tumours and I am sure that more careful search by serial or multiple sections of small tumours would reveal it very frequently The appearances are not to be dismissed as due merely to infiltration of salivary tissue by growth these transition zones show a gradual alteration of the epithelium from normal salivary acini on

or by the subsequent development of a new tumour from predisposed salivary tissue. As Figs 142-144 show, already well-established tumours may show tumour formation from the surrounding salivary tissue still in progress, clearly then removal of the tumour alone at this stage will leave behind potentially neoplastic tissue from which recurrent growth may develop. That multiple neighbouring foci may participate in the formation of a tumour is shown by such specimens as that of Case II, above. Just as the bed of mammary tissue around a fibro-adenoma often contains small satellite fibro-adenomatous foci so the bed of tissue around a salivary tumour may contain multiple potential or actual foci of growth.

An interesting observation of McFarland's (1936) is relevant here. This is that recurrence is more likely to follow removal of small tumours than of large ones, and McFarland advises that tumours should not be removed until they have attained "the size of a lemon". This seeming anomaly is readily understood in the light of what has just been said. The smaller a tumour, the more likely it is that tumour genesis from salivary tissue is incomplete and still in progress or that satellite tumour foci not yet confluent with the main mass are present, and therefore the greater the likelihood that simple enucleation will leave behind the germs of further growth. On the other hand, when a tumour is permitted to grow to a large size before its removal, it is then likely to have incorporated the whole of the potentially neoplastic field of tissue and to have become more completely encapsulated, hence its enucleation is correspondingly less likely to leave behind the seeds of recurrent growth.

In most cases the microscopical structure of a salivary tumour is an unreliable guide to prognosis. On the one hand, recurrence may follow removal of tumours of the most benign looking histological type, and on the other hand cellular active looking growths from which recurrence was anticipated may fail to recur. The "paradoxes" of prognosis have been fully discussed in the several papers by McFarland as well as by Patey. McFarland (1942) found, however, that tumours in which epithelium predominates have a less favourable outlook than those in which mucinous and stromal tissue predominates, the former recurring in 60 per cent of cases and the latter in 38 per cent—a difference which accords well with Zyrhbal's conclusion from tissue cultures that the cells of mucinous areas are of poor proliferative power and viability. McFarland also found that tumours with a predominant "carcinomatoid" structure give a high proportion of recurrences, while the recurrence rate of growths with prominent papillary structure is the highest of all, over 80 per cent. In assessing prognosis, the clinical rate of growth of a tumour should be considered in conjunction with its histological structure: tumours which have increased rapidly and which show carcinomatous appearances microscopically have a bad prognosis.

(12) Metastasis

Lymphatic or blood borne metastases from salivary tumours of the pleomorphic class are rare. Instances have been recorded by Wood, Ahlborn, Fitzwilliams, Ewing, Dockerty and Mayo. Bland Sutton (1906, Fig. 56) depicted a parotid tumour which had been growing slowly for 17 years and which then "grew rapidly and infested the lymph glands, and destroyed the patient in six

Case III—A well circumscribed rounded parotid tumour was removed from a woman of 23 years. The whole tumour which appeared well encapsulated had a similar structure consisting largely of epithelial clusters resembling solid acini distributed around branching tubules and solid epithelial strands in a way generally resembling the relationship of lobules and ducts in normal salivary tissue. Interspersed throughout were islands of normal looking adipose tissue.

In this case I conceive that neoplastic change has overtaken the whole of the salivary epithelium in the susceptible area including both ducts and acini. The acini like clusters are salivary acini which are now neoplastic, the duct like tubules are neoplastic former salivary ducts and the islands of adipose tissue are those of the original parotid gland persisting in the tumour with the same relationships to the now neoplastic tissues as to the former normal tissues. Others who have seen islands of adipose tissue in salivary tumours include Wood (Case 2) and Harvey *et al* (Fig 45).

The question whether the tumours take origin mainly from salivary acini or ducts is of little moment. It is clear that both participate. We have noted the direct transformation of acini into tumour, and the frequent presence in the tumours of duct like structures with characteristic two layered epithelium and specimens like that of Case III point clearly to simultaneous participation of the whole of the epithelial elements in an area of salivary tissue ducts and lobules of acini alike. The mode of origin of the tumours parallels that of mammary carcinoma which frequently arises from a considerable field of mammary epithelium including both ducts and acini.

(9) Stroma and capsule

Even some of those who are satisfied that the tumours are of purely epithelial nature have confused stroma and mucinous and pseudo cartilaginous areas. Again it must be insisted that the latter belong not to the stroma but to the epithelial parenchyma of the tumours. The stromal connective tissues and the mucinous material may mingle intimately producing appearances easily mistaken for mucoid change in connective tissue. Lakes of mucinous secretion often have indefinite borders and seepage of the material into the neighbouring stroma produces mixtures of mucin and collagen with correspondingly variegated staining properties. By using appropriate stains however (e.g. Ehrlich's haematoxylin followed by light counterstaining by picric acid or van Gieson's counterstain), the two ingredients of these mixtures can often be rendered beautifully distinct. As Harvey *et al* have shown elastic as well as collagen fibres may mingle with mucinous matrix. Pools of mucinous secretion may also flow around and isolate blood vessels and haemorrhages into the secretion may occur.

It may be pointed out here that many of the appearances produced by mingling of stromal and parenchymatous elements seen in these tumours are paralleled in mucoid or colloid carcinomas of other organs and in mucoid extravasations such as pseudo myxoma peritonei. In these also we see intimate admixtures of mucinous secretion and connective tissues sometimes accompanied by hyaline changes in the latter.

Changes in the stroma proper of salivary tumours include fibrosis, alteration of elastic tissue, hyaline changes, collections of leucocytes, calcification and rarely, osseous or cartilaginous metaplasia. Increase of collagenous tissue with

metastasizing carcinomas In the case of salivary neoplasms most of the tumours occupy an intermediate or borderline position in the scale of behaviour The prognostic question here should not be, "Is this tumour innocent or malignant?", but 'How innocent, or malignant, is this particular tumour likely to be?' How far we can answer this question has been indicated above

Do relatively benign tumours become malignant, and do recurrences show enhanced malignancy? McFarland (1936) and Patey answered this question



FIG 148—Case V Recurrent growth of cribriform structure infiltrating cervical fascia and platysma muscle ($\times 40$)

in the negative, and concluded that, while different tumours show different degrees of malignancy a single tumour shows little or no change of structure or rate of growth in its recurrences While this is probably true of the majority of tumours there are I believe exceptions Thus in Wood's Case 4 a parotid tumour of slow growth had been present for 53 years and had then grown rapidly in the last few months and microscopic examination showed squamous celled carcinoma in an otherwise typical mixed tumour Bland Sutton's case with metastases referred to above, gave a similar history, and in my Case IV above the recurrent growth and the subsequent metastases showed carcinomatous structure which was not observed in the growth on its first removal The following Case V is also of interest in this respect

Case V—In November 1938 a woman aged 37 attended hospital with a small tumour noticed for 5 months close to the left angle of the mandible This was thought to be a sebaceous cyst and was excised It was a well-defined spherical mass 1 centimetre in diameter microscopically a typical pleomorphic salivary tumour of well differentiated type in which tubular and cribriform structures (like those of Fig. 139) predominated It had a well defined fibrous capsule except at one point where the tumour tissue lay immediately contiguous with parotid tissue The tumour soon recurred and was again operated on in October 1939 when an irregular mass about 3 centimetres in main extent and not separable from the parotid tissue was excised Microscopically this showed a

months The following is an example of metastasis both to lymph glands and by the blood stream

Case IV—In June 1923 a boy of 16 years first noticed a small swelling in the left parotid gland This gradually enlarged until in June 1925 when it was excised it was as large as a hen's egg and somewhat cystic Microscopic examination showed the typical structure of a glandular and mucinous mixed tumour Early in 1930 the patient complained of pain in the ear and at operation a mass of recurrent growth deep in the parotid gland was incompletely removed the microscopical report was mixed salivary gland tumour with carcinomatous areas locally malignant Radium was applied apparently with



FIG 147—*Case IV* Metastatic spheroidal celled growth in a cervical lymph gland ($\times 150$)

good result Late in 1934 enlarged glands first appeared in the neck these increased and were excised in March 1935 and radium was inserted The largest of the excised glands was 4 centimetres in diameter and microscopic examination showed carcinomatous tissue resembling the carcinomatous areas of the recurrent salivary tumour removed in 1930 (Fig 147) Skiagrams now showed scattered small metastases in both lungs and also a probable metastasis in a rib A year later in April 1936 skiagrams showed many large deposits in the lungs and a spherical tumour 6 inches in diameter had developed from the rib The patient died in June at the age of 29 and 13 years from the first appearance of the tumour

(13) Innocent or malignant ?

Because of their slow growth their supposed encapsulation and the rarity of metastasis the pleomorphic salivary tumours have often been classed as 'benign' This fallacious idea cannot be too strongly discouraged Tumours which are often demonstrably not encapsulated which frequently recur after removal which may widely infiltrate surrounding tissues and which occasionally metastasize are far from benign The truth is that here as with many other kinds of neoplasms 'innocent' and 'malignant' are only relative terms and all gradations of behaviour as well as of structure are to be seen between highly differentiated slowly growing innocuous adenomas and poorly differentiated infiltrating and

adenocarcinomas which merge insensibly into the group of anaplastic carcinomas now to be described

ANAPLASTIC CARCINOMAS OF THE SALIVARY GLANDS

I have studied four salivary carcinomas which appeared to be frankly malignant from their onset, growing rapidly, producing metastases, killing within relatively short periods, and consisting of highly cellular rapidly proliferating tissue not at once recognizably related to that of the previous group. From careful study of these four cases, however, as well as from my review of previous reports of salivary carcinomas, I am sure that these growths differ from those of the pleomorphic group only in their rate of growth and degree of malignancy and not in their

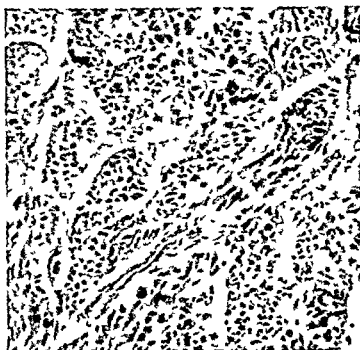


FIG 150—Case VII Polyhedral and spindle-celled epithelial clumps in a metastasis in the adrenal gland ($\times 150$)

histogenesis. My four examples of anaplastic carcinoma, all of the parotid gland, may be briefly described

Case VI—A man aged 61 had had a rapidly increasing mass in the left parotid region for 10 months before he died. *Necropsy* revealed a large hard white parotid tumour with metastases in the cervical lymph glands, many nodules in the skin of the neck and thorax, fewer skin nodules in the lower parts of the trunk and thighs, and multiple metastases in the lungs, parietal pleura, heart (a single nodule in the wall of the left auricle), liver, spleen, ribs, dura mater, abdominal and inguinal lymph glands, and peritoneum. *Histology*—A cellular, spheroidal-celled carcinoma with many mitoses, in places a moderate amount of connective tissue stroma between epithelial strands showing some hyaline change, recalling the appearance of cellular parts of tumours of the pleomorphic group.

Case VII—For 16 months before he died, a man aged 71 had had a rapidly increasing left parotid tumour which attained an enormous size. *Necropsy* showed a huge solid white tumour with satellite skin nodules around it, metastases in the cervical and upper

structure similar to the previous specimen but was infiltrating the surrounding parotid and cervical tissue (Fig 148). X ray therapy was carried out. The tumour recurred again early in 1941 and in May an ill defined mass of growth about 4 centimetres in diameter was excised. Microscopically this showed in addition to some cribriform structure many areas of undifferentiated spheroidal celled carcinomatous growth (Fig 149). In May 1942 the patient developed pleural effusion and cough and a skiagram strongly suggested the presence of small scattered metastases in the lungs.

The foregoing observations show that on occasions salivary tumours do display accelerated rates of growth with enhanced malignancy sometimes demonstrably



FIG. 149.—Case V.—Further recurrence of growth of undifferentiated carcinomatous structure ($\times 75$)

accompanied by structural de differentiation. I agree however that this change is improperly described by saying that benign tumours become malignant: the tumours are malignant all along but their rate of proliferation and degree of malignancy may sometimes show more or less abrupt increases. Whether such increases are ever due to surgical trauma is doubtful. Woods and Bland Sutton's cases showed accelerated growth prior to operation.

Because these tumours are always either potentially or actually malignant I cannot concur with Harvey *et al.* and other workers in calling them all adenomas. This title though commendable in so far as it emphasizes the simple glandular origin and nature of the growths gives a false estimate of their benignancy. If we are to have a reasonably correct designation for the whole group formerly called mixed tumours it cannot be made any simpler than pleomorphic adenomas and adenocarcinomas. This recognizes the mixed or variable structure of the tumours and the variable behaviour which they display ranging from the rare benign adenomas to frankly malignant

These four tumours, though highly malignant, nevertheless show traces of the structural characters familiar in the pleomorphic tumours, namely hyaline changes in the stroma, secretion by the tumour cells (signet-ring cells in Case VII) and spindle celled epithelial masses. I believe that no sharp line of demarcation can be drawn between the most malignant tumours of pleomorphic type and the still more malignant growths like those just described, these merely represent the extreme end of the scale of malignancy. I believe that, excluding the adeno-lymphomas, all salivary tumours have in the words of Fry, 'the same essential structure, the difference between them being a difference in degree of malignancy and in the amount of secondary changes'.

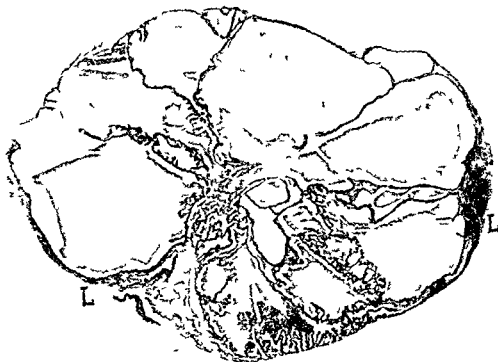


FIG 152—Case X Whole section of adeno-lymphoma, showing its polycystic and papillary structure and peripheral areas of lymphoid tissue (L) ($\times 5$)

Salivary sarcomas

This is the proper place to refer briefly to the supposed occurrence of sarcomas in the salivary glands. I have yet to see a report of a case in which I could accept this diagnosis as even probable. As was noted early in this chapter, the pleomorphic tumours, especially those with diffuse mucinous areas, were formerly often classed as 'sarcomas' or myxosarcomas. Excluding these and excluding also cases of secondary leukaemic and lymphosarcomatous infiltration of salivary tissue (one cause of Mikulicz's syndrome), there remain only very rare instances of supposed 'sarcoma' of the salivary glands, and examination of these makes it clear that in most or all of them the tumours were not sarcomas but anaplastic carcinomas like those described above. As long ago as 1910,

mediastinal lymph glands and in the lungs liver spleen and both adrenal glands. The primary tumour had directly invaded the thyroid gland and the internal jugular vein. *Histology*—A highly cellular carcinoma of rather variable structure. Parts consist of large polyhedral and irregular cells arranged diffusely and with little tendency to epithelial grouping some of the cells are of signet ring form containing droplets of secretion. Other parts consist of elongated and spindle shaped cells often arranged in epithelial clumps (Fig 150). Mitoses are very numerous sometimes multipolar and some of the tumour cells are large irregular and multinucleated. Stroma is scanty.

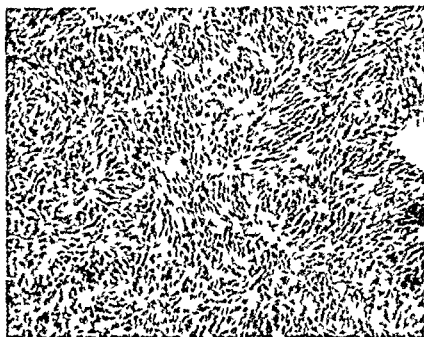


Fig 151 —Case VIII Spindle-celled sarcoma like structure of a metastasis in the lung ($\times 150$)

Case VIII—A woman 37 years old at her death had first noticed a lump in the left parotid area 3½ years previously. Operation 2 months after this disclosed a friable vascular tumour the size of a golf ball in the substance of the parotid gland microscopically a cellular anaplastic carcinoma. Repeated radium treatments were carried out each time with temporary benefit followed by recurrence of the growth. *Necropsy* showed a huge soft parotid tumour with metastases in the lungs liver both adrenals retroperitoneal tissues and a single metastasis 6 centimetres in diameter in the right breast. No metastases were found in lymph glands. *Histology*—Parts of the tumours show clumped spindle-celled groups similar to those of Fig 150 but the bulk of the tissue consists of diffusely arranged spindle-cells resembling a spindle-cell sarcoma (Fig 151). Mitoses are plentiful and stroma scanty.

Case IX—A man of 78 years had noticed a mass growing in the parotid region for 7 months. On examination this was a large mass invading the skin and adherent to deep structures. Excision was attempted but was incomplete and the patient died of recurrence a few months later (no necropsy). The excised mass was 6.5 centimetres in diameter partly well defined partly infiltrating surrounding tissues including the sternomastoid muscle. The tissue was firm and white with degenerated and haemorrhagic areas but no mucinous areas or other evidence of an antecedent mixed tumour. *Histology*—A cellular spheroidal-celled and spindle-celled carcinoma most of which shows definite epithelial clumping with intervening strands of partly hyaline connective tissue but with other parts more diffuse in structure. Mitoses are many and there are some large irregular multinucleated tumour cells.

Microscopically it had the characteristic structure of a cystic papillary adeno-lymphoma (Fig 153). Most of the lymphoid tissue lay around the periphery beneath the capsule strongly suggesting that the growth occupied a lymph gland. There was no recurrence 4 years after removal.

Case XI—A man of 57 years had noticed an enlarging lump below the left ear for 2 years. Examination showed a rounded mobile swelling 4 centimetres in diameter, and operation disclosed a thick walled cystic mass with turbid yellow contents thought to be an enlarged, probably tuberculous lymph gland. Microscopic examination of a piece of excised tissue however showed the typical structure of cystic papillary adeno-lymphoma with abundant lymphoid tissue in the stroma.

(1) Clinical characters

(a) Age incidence

On the average, adeno lymphomas appear later in life than the pleomorphic salivary tumours. The ages in decades of the cases collected by Plaut were

Decades	-	-	1	2	3	4	5	6	7	over 70
No of cases	-	-	2	2	1	5	13	20	13	5

Youngest, 2½ years, oldest 92, average 52 years

(b) Sex

In sharp contrast with the pleomorphic tumours, adeno lymphomas show a great preponderance of males—in Plaut's collected cases, 50 males to 12 females. It would be of interest to determine whether or not heterotopic salivary tissue in lymph glands occurs more often in men than women.

(c) Situation

With few exceptions the tumours are related to the parotid gland, being situated usually quite superficially and often separate from the gland, or occasionally in its substance. A few of the tumours have been related to the submaxillary gland. Two cases with bilateral tumours have been reported (Plaut).

(d) Duration and rate of growth

Most of the tumours are of slow growth. The pre-operative duration varies from a few weeks to many years, with an average of about 6 years. Even after long duration some tumours are still quite small, e.g. in the fourth case of Car michael *et al* the tumour was only 2 centimetres in diameter after 30 years. On the other hand some of the tumours have attained a large size in much shorter periods.

(e) Prognosis

With rare exceptions the tumours are encapsulated, easy to shell out completely, and quite benign. Recurrence is unusual, and frankly malignant characters, as in the cases of Stohr and Risak, and Sobolew (references by Plaut), are rare.

Chevassu deprecated the tendency to give the name sarcoma to every malignant tumour the elements of which are arranged diffusely. This warning still often neglected along with the histology of the four examples of anaplastic carcinoma described above is all that need be said of sarcoma of the salivary glands.

SALIVARY ADENO LYMPHOMAS

These relatively rare growths, which constitute less than 10 per cent of all salivary tumours, are highly distinctive and unrelated to the common pleomorphic adenomas and adenocarcinomas. Under the quite appropriate alternative name of *papillary cystadenoma* they were first described in 1910 by Albrecht and Arzt, who noticed the close resemblance of their epithelium to that of salivary ducts. In 1923 Nicholson reported the first English cases describing the tumours as



FIG 153—Case X Adeno lymphoma ($\times 80$)

adenomas of heterotopic salivary tissue in the preauricular lymph glands. The best general account of these tumours is that of Carmichael, Davie and Stewart (1935) who reviewed 26 previously reported cases and added 8 of their own. By 1942 Plaut was able to bring the total number of reported cases up to 64. I have studied two specimens of typical adeno lymphoma the details of which are briefly as follow.

Case X—A man of 67 years had had a slowly enlarging mass below the left ear for 2½ years. Excised intact this was an encapsulated ovoid mass resembling an enlarged lymph gland 2.5 \times 2 \times 2 centimetres. On section it consisted of several large cystic spaces occupied by gelatinous material and into which projected some fringes of papillary growth. Some crescentic areas of solid tissue lay at the periphery in places (Fig. 152).

'onkocytoma' should be discarded Kraissl and Stout's suggestion that adeno lymphomas arise from vestiges of orbital salivary glands is wholly speculative

REFERENCES

- Ahlbom H E (1935) *Mucous and Salivary gland Tumours* Stockholm
 Albrecht H and Arzt L (1910) *Frankfurt Z Path* 4 47
 Ealme H (1912) *Brit Med J* 1 1292
 Bland Sutton J (1906) *Tumours Innocent and Malignant* p 57 London
 BOTTNER O (1921) Das sezernierende Epitheliom (die sog Mischgeschwulst) der Mundspeicheldrüsen *Beitr path Anat*, 68 364 (An excellent account upholding epithelial origin)
 CARMICHAEL, R, DAVIE, T B, and STEWART M J (1935) Adenolymphoma of the salivary glands *J Path Bact* 40 601 (An excellent account)
 Chevassu M (1910) *Rev de Chir* 41 145 450
 Davis L J (1935) *J Path Bact* 41 289
 De M N and Tribedi B P (1939) *J Path Bact* 49 429
 DOCKERTY, M B, and MAYO C W (1942) Primary tumors of the submaxillary gland with special reference to mixed tumors, *Surg Gyn Obst* 74 1033
 Eggers H E (1928) *Arch Path* 6 378
 Ewing J (1940) *Neoplastic Diseases* p 793
 Fick J (1909) *Virchows Arch* 197 472
 Fitzwilliams D C L (1935) *Lancet*, ii 769
 FRY R M (1928) The structure and origin of the mixed tumours of the salivary glands *Brit J Surg* 15 291 (A valuable study showing the epithelial nature of the tumours)
 Harvey W F Dawson E K and Innes J R M (1938) *Edinb Med J* 45 275
 Hempleman L H, and Womack N A (1942) *Ann Surg* 116 34
 Jaffe R H (1932) *Amer J Cancer* 16 1415
 Kaufmann E (1929) *Pathology* p 603 Reimann's translation Philadelphia
 Kraissl C J and Stout A P (1933) *Arch Surg* 26 485
 Krompecher E (1908) *Beitr path Anat* 44 51 88
 Kux E (1931) *Virchows Arch* 280 175
 Lepp H (1939) *Beitr path Anat* 102 164
 MacCallum W G (1940) *A Textbook of Pathology* p 1216 Philadelphia
 McFarland J (1924) *Surgical Pathology* p 87 Philadelphia
 McFarland J (1926 and 1942) *Amer J Med Sci* 1926, 172 804 and 1942 203, 502
 McFarland J (1936) *Surg Gyn Obst* 63 457
 Muir R (1941) *Textbook of Pathology* p 258 London
 Nicholson G W (1922) *Guy's Hosp Rep* 72 333
 Nicholson G W (1923) *Ibid*, 73 37
 PATEY D H (1931) The mixed tumours of the salivary glands *Brit J Surg* 18 241 (A good account especially of the histology and prognosis)
 PLAUT, J A (1942) Adenolymphoma of the parotid gland *Ann Surg* 114 43 (Tabulates reported cases)
 Schilling F (1921) *Beitr path Anat* 68 139
 Schutz, C B (1926) *Amer J Path* 2 153
 Skorpil F (1940) *Virchows Arch* 306 714
 Steinhardt G (1933) *Virchows Arch* 289 624
 Stobie H (1935) *Proc Roy Soc Med* 28 739
 Street A (1913) *Brit Med J* i 1047
 Wilson L B and Willis B C (1912) *Amer J Med Sci* 143 656
 Wood F C (1904) *Ann Surg* 39 57 207
 Yen F C (1915) *J Amer Med Assoc* 64 1238
 ZYMBAL W E (1933) Histologische und experimentelle Untersuchungen über die Geschwülste der Speicheldrüsen *Beitr path Anat* 91 193
 der Speicheldrüsen *Beitr path Anat* 91, 113

(2) Structure

(a) *Naked eye characters*

The tumours are rounded, ovoid or slightly flattened, with an even or slightly lobulated smooth surface and a distinct capsule. On section, they may be wholly solid but are much more often partly cystic. The tumour tissue forms shaggy papillary fringes or masses projecting into the cystic spaces. The cyst contents may be mucoid, milky, or turbid resembling liquid caseous material or pus in which event the surgeon may easily mistake the tumour for a tuberculous lymph gland as in my Case XI.

(b) *Histology*

The microscopic structure of the growth is highly distinctive—showing a more or less intimate mixture of lymphoid stroma with a characteristic epithelial parenchyma which forms tubules or lines the cystic spaces and the branching intra-cystic papillary projections. The epithelium closely resembles that of the medium sized ducts of the salivary glands. It consists of a double layer of cells comprising a regular palisade of tall columnar eosinophilic cells which reach the free surface and have their nuclei in an even row towards the free margin and a basal layer of smaller irregular cells usually fewer in number and less regularly spaced than the tall cells. The stroma between the epithelial tubules or cysts or forming the cores of the branching papillary structure is infiltrated by few or many lymphocytes or beset with prominent lymphoid follicles. Some plasma cells or eosinophil leucocytes may mingle with the lymphocytes. Dense fibrous stroma may be present in places, and the capsule of the tumour is fibrous and well defined.

(3) Histogenesis

Nicholson's view that these tumours arise from heterotopic salivary tissue in lymph glands has already been mentioned. Before reporting his two cases Nicholson had already (1922) noted the observation of Neisse that heterotopic salivary tubules are frequently present in the pre-parotid lymph glands of infants and had himself reported an example of persistence of such tubules in an adult. Moreover he had no doubt that the two tumours which he described were indeed within lymph glands, an opinion which the structure in my Case X also strongly supports. The frequent separateness of the tumours from the parotid gland and the frequency with which at operation they are regarded as enlarged lymph glands also support Nicholson's view which indeed has gained wide acceptance and which I am satisfied is the correct one. Adeno lymphoma, whilst not an ideal name is a brief and descriptively convenient one expressing the combination of epithelial glandular and lymphoid tissue in these tumours though papillary cystadenoma and salivary adenoma of lymph glands are also quite appropriate.

The opinion of some workers that the tumours arise from branchial remains is groundless as well as superfluous. So also is the view that they arise from a special kind of epithelial cell seen in the salivary gland of old people the 'pykno-cyte' of Zimmermann or 'onkocyte' of Hamperl and Jaffe's ugly name

irregular glandular spaces. In places the epithelium has a prominent cuticular margin. The cytoplasm is distinctly eosinophilic and foamy in structure because it contains



FIG 154—*Case VI* Nasal adenocarcinoma ($\times 120$)

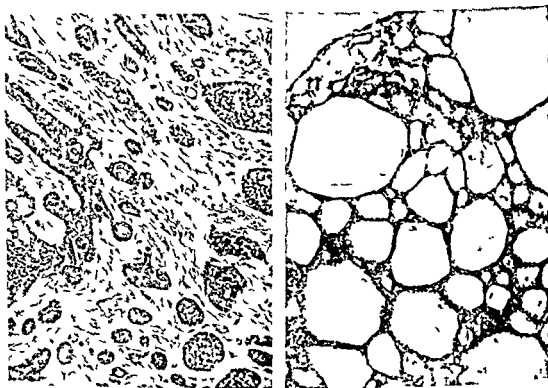


FIG 155—*Case VII* Nasal adenocarcinoma ($\times 120$)

CHAPTER 18

EPITHELIAL TUMOURS OF THE NASAL AND PARANASAL CAVITIES

ALTHOUGH most parts of the nasal and paranasal cavities are lined not by squamous stratified epithelium but by pseudo stratified respiratory epithelium it is not surprising that many of the epithelial tumours of these cavities are of squamous structure. The nasal epithelium is derived mainly from the ectoderm, it persists in the squamous form in the region of the nostrils and as in the bronchi the respiratory epithelium readily undergoes squamous conversion in neoplasms. Some tumours, however, retain the structure of the pseudo stratified epithelium, with or without cilia. Other tumours the nasal adenocarcinomas clearly arise from the nasal glands. A special group of tumours involving the maxillary antrum and possessing a variable structure often described as resembling the cystic basal cell carcinomas of the skin or the so-called 'mixed tumours of the salivary glands' still cause confusion. I shall advance reasons for believing many of these to be 'adamantinomas' arising from the paradental epithelial residues. It will be useful to outline first my own observations of nasal tumours.

ELEVEN PERSONALLY STUDIED NASAL EPITHELIAL TUMOURS

(1) Epidermoid carcinoma

Case I—Male aged 56. Pieces of tumour curetted from the sphenoid and ethmoid sinuses showed active squamous-cell carcinoma.

Case II—Female aged 64. Masses of tumour removed from the maxillary antrum showed well differentiated squamous-cell carcinoma.

Case III—Male aged 69. Masses of tumour removed from the maxillary antrum showed non-cornifying squamous-cell carcinoma.

Case IV—Female aged 67. Pieces of tumour removed from the maxillary antrum showed diffuse cellular carcinoma of epidermoid type.

Case V—Male aged 54. *History*—Pain and swelling of face for 15 months. *Necropsy* showed right antrum and surrounding bone replaced by a huge firm growth with great enlargement of the face and invasion of the skin of the cheek and eyelid. Tumour deposits were present in the upper posterior cervical lymph glands but there were no remote metastases. *Histology*—Both primary growth and lymph nodal metastases showed diffusely cellular anaplastic epidermoid carcinoma in parts so undifferentiated as not to be recognizably epithelial in character.

(2) Adenocarcinoma

Case VI—A man aged 68 had noticed increasing nasal obstruction and discharge for 4 years and more recent swelling of the nose and left side of the face. Examination showed the left nasal cavity to be distended by a mass of friable growth and skiagrams showed enlargement and opacity of the maxillary sinus. Deep X ray therapy produced no noticeable improvement in the tumour and 5 years later the patient was reported by relatives to have extensive ulcerating growth. *Histology* (Fig 154)—Pieces of the nasal portion of the tumour show well-differentiated adenocarcinoma consisting of low columnar or pyramidal cells arranged in a single layer around well-defined acini or

Case VII—A man aged 70 had had symptoms of an enlarging nasal and antral tumour for 3 years. Examination and exploratory operation showed large masses of growth in the right half of the nasal cavity and in the antrum. the anterior bony wall of the antrum was destroyed and a mass of growth projected externally. *Histology* (Fig 155)—Pieces of tissue removed from the nasal, antral and externally projecting parts of the growth all show similar characters. The tumour is an adenocarcinoma with areas of acinar structure.

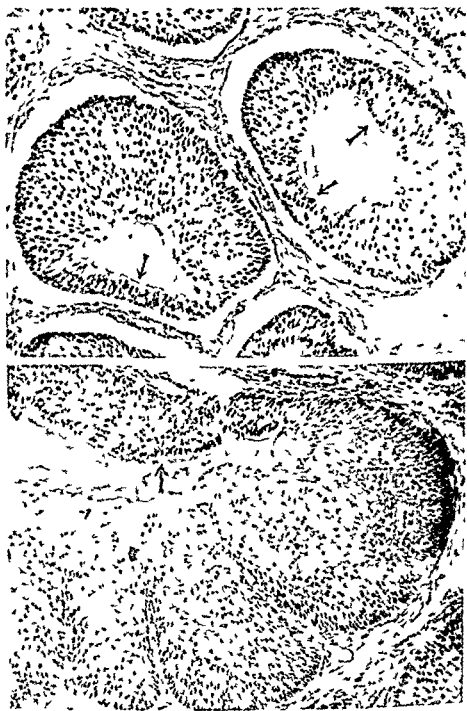


FIG 158—*Case X* Details of nasal "papilloma" the epithelium of which is partly of ciliated respiratory type (marked by arrows) and partly of squamous stratified type ($\times 120$)

multiple fine droplets of secretion which are often distributed radially in the cells. The nuclei are basal spherical fairly uniform in size about 8μ in diameter each with a single nucleolus and an evenly stained fine chromatin meshwork. mitotic figures are rare. The acinar cavities contain some eosinophilic secretion.



FIG 156—Case IX Nasal mucoid adenocarcinoma ($\times 120$)



FIG 157—Case X Nasal papilloma ($\times 6$)

had caused a perforation into the antrum and blood had come from the nose) Operation disclosed a friable mass of growth distending the antrum, this was easily removed except along the nasal wall to which it adhered firmly Radium was inserted *Microscopical examination* (Fig 159) showed the tumour to consist of well defined small and large masses and trabeculae of epithelial tissue in places closely like those of the cystic basal-cell carcinomas of the skin in other places resembling adamantinoma of the jaws The marginal parts of the masses were formed of closely set palisades of cubical or columnar cells The cells of the central parts of the masses were less compact with many rounded intercellular spaces which either appeared empty or contained some pale eosinophilic



FIG 159B—Case XI Basal cell carcinoma (adamantinoma) of antrum ($\times 120$)

secretion These spaces gave many of the epithelial masses a cribriform pseudo-glandular appearance but as in the pleomorphic tumours of the salivary glands and in adamantinomas, the cells lining the spaces were flattened and showed no glandular

similar to that of Case VI but with many areas of imperfectly differentiated structure consisting of irregular gland spaces lined by double or triple layers of epithelial cells solid epithelial cords or masses or masses riddled by dilated acinar spaces giving a cerebriform or honeycombed appearance. Mitotic figures are present in moderate numbers.

Case VIII—Male aged 68. Pieces of tumour removed from the ethmoid region showed adenocarcinoma resembling that of the previous case.

Case IX—A small sessile greyish tumour 1 centimetre in diameter was removed from the lateral wall of the nasal cavity of a man of 75 years. *Histology* (Fig 156)—It is a well differentiated papillary mucoid adenocarcinoma consisting of convoluted and branching layers of columnar-cell epithelium including many mucus-containing goblet cells along with quantities of extra-cellular mucinous secretion. Most of the epithelium is single layered but in places it appears pseudo stratified. No ciliated cells can be found. Moderate numbers of mitotic figures are present.

(3) Papillary respiratory epithelial carcinoma 'papilloma'

Case X—A mucous polyp of unrecorded duration was removed from the nasal cavity of a man of 50 years. *Microscopically* (Figs 157 and 158) it proved unexpectedly to be a papillary carcinoma clearly derived from the ciliated pseudo-stratified respiratory epithelium. The surface of the growth and folded branching spaces within it were clothed by a thick layer of epithelium partly of typical ciliated pseudo stratified type and partly of stratified squamoid type the two alternating and merging with one another. Where the squamous changes were prominent there were many solid clumps and columns of epithelium occupied centrally by large masses of swollen polygonal and squamous cells but without cornification. Mitotic figures were plentiful. Two months later a recurrent growth was removed from the maxillary antrum and this showed similar characters with however more advanced squamous change and a coarser papillary structure.



FIG 159A—Case XI Basal-cell carcinoma (adamantinoma) of antrum ($\times 120$)

(4) Carcinoma of so-called basal-cell type adamantinoma

Case XI—A woman aged 46 complained of enlargement of the left side of the face of 4 years duration. Recently a swelling of the alveolar ridge had necessitated cutting away part of her dental plate and the left side of her nose was growing larger. (When she had had all her teeth removed 21 years previously extraction of the left upper incisor

anaplastic ones, and the latter may be so cellular and diffuse in structure that parts of them may be microscopically indistinguishable from sarcoma, as in my Case V. Epidermoid carcinomas are seldom of long duration, and the more anaplastic often kill within a few months of the onset of symptoms. Metastasis to the upper deep cervical lymph glands is not unusual in the later stages, but remote metastasis is not commonly recorded. MacComb and Martin reported metastases in 19 of 65 cases of malignant nasal tumours (29 per cent), most of these were in the cervical lymph glands, remote metastasis occurred in only 6 cases, to lungs, bones, liver and brain, in all but one case with metastases the tumours were epidermoid carcinomas. Ringertz saw metastases in 32 of 119 squamous cell carcinomas (27 per cent). Gaehtgens (1933) saw a case with multiple blood borne metastases in the viscera and bones from a small unsuspected primary nasal tumour.

(2) Adenocarcinomas

The structure of some of these, as in my Cases VI, VII and VIII, makes it clear that they have arisen from the glands of the nasal mucosa. Highly mucoid tumours, such as that of Case IX, may arise rather from the goblet celled surface epithelium. Parts of some of the adenocarcinomas show a variety of acinar, mucoid, cribriform and solid structures, resembling that seen in the pleomorphic salivary tumours. The rate of growth is decidedly less than that of the epidermoid tumours, durations of several or many years being common, as in Cases VI and VII. The slower growing, best differentiated glandular growths of the nasal mucosa, Ringertz and others have called 'adenomas', admitting, however, that recurrence is frequent and that the distinction from carcinoma is indefinite. The adenocarcinomas eventually destroy the surrounding bones, infiltrate soft tissues, and ulcerate in the mouth, pharynx or externally. I do not know of any adequately substantiated examples of metastasis, MacComb and Martin mention one case, but without details. None of Ringertz's 10 cases showed metastasis.

(3) Basal-cell carcinomas and adamantinomas

Adamantinomas are, of course, not primarily nasal tumours, but from the close anatomical relationship of the roots of the maxillary teeth to the floor of the antrum of Highmore, it is obvious that tumours derived from the maxillary paradental residues must in many cases grow into the antral cavity. (For examples see the cases of Vorzimer and Perla (1932), and Simmons (1928) Nos 3 and 9). Yet this is often overlooked by pathologists who accordingly continue to confuse such tumours with 'cystic adenoid carcinoma', 'salivary tumour', or 'basal cell carcinoma', as in my Case XI above. Geschickter's list of nasal and paranasal tumours did not mention adamantinoma and I suspect that some at least of his 15 'cystic basal cell carcinomas' (including that of his Fig 13), and also the supposed 'adenocarcinoma of Schneiderian type' depicted in his Fig 18 may really have been adamantinomas. The diversity of structure and cystic change seen in adamantinomas and the close resemblance of some of these to structures seen in basal cell carcinomas of the skin and in the pleomorphic salivary tumours account for the variety of designations of the antral adamantinomas when their true nature is not recognized. Careful search of several different

orientation. Some of the epithelial masses contained a loose meshwork of cells resembling the stellate reticulum of adamantinomas. No prickle cells or cornification could be found. Mitotic figures were scanty. *Comment*—This tumour was at first identified by me as a cystic adenoid basal-cell carcinoma of the antrum and I realized its true identity only later. If it had predominantly involved the alveolar region of the jaw it would undoubtedly have been correctly identified at first. The history of injury to the antrum during extraction of the teeth serves to remind us how close the roots of the teeth are to this cavity, and therefore how readily a tumour derived from the paradental residues might extend primarily into the antrum.

STRUCTURAL TYPES OF NASAL TUMOURS AND THEIR BEHAVIOUR

These have been exemplified in the foregoing cases. The monograph of Ringertz (1938) contains much valuable information and excellent photomicrographs. Geschickter (1935) also has described and depicted examples.

(1) Epidermoid and respiratory papillomas and carcinomas

(a) *Papillomas*

Papillomas clothed by squamous stratified or respiratory epithelium are rare and, as with most other papillary growths of mucous membranes, their benignancy open to doubt. An excellent paper by Kramer and Som (1935) reviewed 85 tumours of this kind. These affected males more often than females, occurred mainly in middle age and arose more often in the paranasal sinuses—usually the ethmoid or maxillary—than in the nasal cavity. There was often a long history of nasal infection, but the causative influence of this was doubtful. All kinds of epithelium, respiratory squamous and transitional, might be seen in one tumour. Recurrence after removal was usual because there is usually diffuse involvement of the nasal mucosa—true papillomatosis. The interval prior to recurrence varied greatly and might be as long as 8 years. Repeated recurrences might take place during many years without the supervention of invasive characters or histological malignancy. Carcinomatous change was however a common termination. Ringertz's account of 10 new cases confirmed the greater incidence in males, the occurrence of multicentric papillomatosis, the variety of the epithelium, the proneness to recur and to become malignant. It seems clear that no sharp distinction can be made between benign papillomas and papillary carcinomas. Tumours IX and X above would certainly have been included as 'papillomas' by Kramer and Som. Case X shows how readily parts of a tumour of respiratory epithelial type may assume a well differentiated squamous papillary architecture.

(b) *Epidermoid carcinomas*

These, usually of the ordinary squamous celled type and less often of the lympho-epithelioma type, are the commonest nasal tumours. The maxillary antrum is their most frequent site of origin, but lympho-epitheliomas are more often nasal than antral (Geschickter). The cancerous epithelium may exhibit to varying degrees the characters of respiratory pseudo-stratified epithelium (excellent photos by Ringertz) but squamous change is nearly always prominent in malignant tumours. Like the carcinomas of the fauces and pharynx, the nasal carcinomas differ greatly from one another in their degrees of differentiation. Tumours of highly keratinizing type are less frequent than poorly differentiated

of arsenic smelters, the flock had had attacks of arsenical poisoning, and arsenic was present in small quantities in the tumours and organs of the cancerous animals. Nieberle also referred to endemic nasal tumours in horses and cattle, reported from Sweden by Sternstrom and Magnusson. The nasal and paranasal cavities are among the commonest sites of carcinoma in horses (Feldman, 1932). Experimental investigation of the possible carcinogenic action of inhaled nickel, chromium, arsenic and their compounds, and of other occupational fumes and dusts is needed.

REFERENCES

- Bridge J C (1939) *Annual Report of Chief Inspector of Factories*, p 61 H M Stationery Office
 Feldman W H (1932) *Neoplasms of Domesticated Animals* pp 292-295 Philadelphia
 Gaeltgens G (1933) *Frankfurt Z Path* 46 1
 Geschickter, C F (1935) *Amer J Cancer* 24, 637
 KRAMER R, and SOM, M L (1935) 'True papilloma of the nasal cavity', *Arch Otolaryng* 22 22 (A valuable review with illustrative cases and good photomicrographs)
 MacComb W S and Martin H E (1942) *Amer J Roentg* 47, 11
 Newman D (1890) *Glasgow Med J* 33 469
 Nieberle K (1939) *Z Krebsforsch* 49 137
 RINGERTZ, N (1938) Pathology of malignant tumors arising in the nasal and paranasal cavities and maxilla *Acta Oto laryng*, Supp XXVII (An admirable monograph, with many case reports many excellent microphotographs and a full bibliography)
 Simmons C C (1928) *Ann Surg* 88, 693
 Stephens G A (1933) *Med Press* 187 194
 Vorzimer, J, and Perla D (1932) *Amer J Path* 8 445

sections of a tumour may be necessary in order to discover typical adamantinomatous epithelium with well formed stellate reticulum, this applied to my Case XI

The ease with which adamantinomas may be confused with 'basaliomas' and "salivary tumours" was recognized by Ringertz, who spoke of a 'basalioma type' of adamantinoma and who said "if the whole adamantinoma is of the basalioma type, it is impossible to distinguish the growth histologically from a salivary gland tumor. And again, he rightly insisted 'in the case of maxillary tumors it is often impossible to determine whether the tumor arose in the alveolar process or in the sinuses' "

✓ I do not deny that true nasal tumours of basal cell type occur. Indeed in view of the closely similar structures to be seen in basal cell carcinomas of the skin, the pleomorphic salivary tumours and the adamantinomas it might be expected that some of the tumours of the nasal epithelia would display similar structures. But it is certain that these tumours and the antral and nasal adamantinomas have often been confused with one another, especially when only one or two micro sections of the tumours have been examined and which of any given worker's diagnoses are correct and which incorrect it is often impossible to say. I believe that the more thoroughly tumours of basal cell appearance are examined the higher the proportion of them that will be recognized as being adamantinomas.

The behaviour of the antral adamantinomas resembles that of their mandibular and alveolar counterparts. They are of slow growth, distending and destroying the surrounding bone, difficult to eradicate and usually fatal, but rarely producing metastases.

THE CAUSATION OF NASAL TUMOURS

The age distribution of nasal and paranasal carcinomas is about that of carcinomas in general: they are unusual in young people and most prevalent in the sixth and seventh decades. The mean age of my 10 cases was 64 years and the mean age of MacComb and Martin's 65 patients with malignant nasal tumours 58 of which were carcinomas was 55 years. In most series of cases there have been more males than females—8 to 2 in my series, 41 to 24 in MacComb and Martin's—but in Ringertz's series there were more women than men.

The evidence that either the ordinary infections of the nasal cavity and sinuses or the presence of simple inflammatory polypi predisposes to carcinoma is inconclusive, but Ringertz believes that there is adequate evidence of such a predisposition. In Gaetgen's case the patient had had rhinoscleroma six years earlier and the rest of the nasal mucosa showed polypoid changes and squamous metaplasia, and two of MacComb and Martin's cases of epidermoid carcinoma had rhinoscleroma.

There is evidence that occupational exposure to certain inhaled irritants is a causative factor in some cases. It is known that the inhalation of chromate dust or fumes may produce perforating ulcers of the nasal septum, and in 1890 Newman reported a large adenocarcinoma of the nares of a man aged 47 years who had worked for 20 years in a chromate plant and who had a characteristic perforation of the septum. Stephens (1933) and Bridge (1939) refer to cases of nasal cancer in nickel workers. Nieberle (1939) reported endemic nasal adenocarcinomas in a flock of sheep: the animals were within the fume and dust zone

carcinomas, the correct diagnosis of many of the cases so recorded will be plain. It is of course now well recognized that most of the erstwhile "mediastinal oat cell sarcomas" are secondary deposits of bronchial carcinoma (Barnard, Simpson, Bonser). It is still not sufficiently recognized that secondary growths in the pericardium, pleura or cervical lymph glands may easily be mistaken for primary tumours (Chapter 10), and that other errors of pathological diagnosis are being made by those who are unaware of the structural versatility of bronchial cancer and the ease with which small primary growths may escape detection at necropsy (see Willis 1938, Turner and Willis, 1938).

(c) Modern diagnostic methods, especially radiography and bronchoscopy, must have brought about, not only improved diagnosis of lung cancer, but an increasing general acquaintance with the disease and its behaviour.

(d) Pulmonary carcinoma will, of course, have shared in the general increase of cancer because of the increased proportion of old people in the population. Comparison of early and recent necropsy series as regards the frequency of lung cancer have often failed to take account of the age compositions of the respective series. Since the disease is much commoner in men than in women, allowance must also be made for the sex ratios of necropsy series to be compared.

(e) Of significance are the analyses of necropsy records made by Bonser (1928 and 1934) and by Passey and Holmes (1935). Bonser's analysis of the necropsies during 41 years at Leeds, where an unusually high proportion of fatal cases were examined, showed no increase in the incidence of intra-thoracic cancer when considered with respect either to the total number of necropsies, the total number of cancer cases, or the total number of admissions to hospital. Passey and Holmes studied the incidence of intra-thoracic cancer in the necropsy records of 16 major teaching hospitals in Great Britain; in 8 hospitals there was no evidence that this was increasing, in 3 the results were inconclusive, while in 5 institutions which did show an increase there were special circumstances which may have been responsible. Sitsen and Steiner also are among the many pathologists who deny that there is any satisfactory evidence of a real increase in the incidence of lung cancer during recent years. The suspicion is that where such increase has appeared to have been conspicuous, there was formerly a low standard of accuracy of pathological diagnosis and that the standard has improved with the passage of time.

For the foregoing reasons, comparisons of early and recent clinical or necropsy estimates of incidence, or comparisons of the findings in different countries or in different hospitals, must be quite unreliable. So much depends on the personal experience of the clinicians and pathologists concerned and current journals contain evidence enough that a uniformly high standard of diagnosis of this elusive disease has not yet been attained by either. Now that the properties of the disease are becoming better known, however, its true frequency and trend in a given community or institution might be ascertainable by meticulously careful and complete necropsies performed by skilled pathologists on all fatal cases over a period (probably 20 or 30 years) sufficient to obviate chance fluctuations.

(2) Age incidence

Pulmonary carcinoma on the average affects rather younger people than most

CHAPTER 19

EPITHELIAL TUMOURS OF THE TRACHEA, BRONCHI AND LUNG

PULMONARY carcinoma, the main topic of this chapter is of special clinical and pathological interest because of the frequent difficulties and errors of diagnosis which it occasions its variety of structure, its abundant metastases, its supposed increase in frequency, and the variety of its possible causative factors. Because of the frequent misdiagnosis of the disease, only fully proved necropsy records are of any value for the analysis of its properties. From the great number of necropsy series which have been published those of the following writers will be found valuable—Fried (1925 1927 and 1935) Duguid (1927) Kikuth (1925) Simpson (1929) Karsner and Saphir (1930) Maxwell (1930), Bonser (1928 and 1934) Kraft (1934), Frissell and Knox (1937) Monographs by Davidson (1930) and by Simons (1937) give good outlines of the clinical aspects of the disease, and Chapter IV of Hueper's book (1942) contains an excellent account of possible causative factors, with plentiful references. My own necropsy experience of 84 cases all of which were fully and carefully studied will be cited freely in this chapter. Bronchial adenoma and other relatively benign types of growth will be considered at the end of the chapter.

FREQUENCY AGE SEX RACE AND SPECIES INCIDENCE

(1) Frequency and its supposed increase

Whereas up to the second decade of this century, carcinoma of the lung was regarded as a relatively rare disease it is now recognized as one of the commonest forms of cancer, accounting for between 5 and 15 per cent of cases of carcinoma in most recent necropsy series. Is the increase real or only apparent? Attempts to answer this question have reached contradictory conclusions (Wahl Bonser Passey and Holmes Kennaway and Kennaway Simons Hueper Steiner). Having read many of the contributions to the controversy and having surveyed my own experience of the diagnostic errors made in this disease my opinion is that it is not possible either to affirm or to deny that there has been a real increase. My reasons for this non committal opinion are briefly as follow

(a) Clinical misdiagnoses even with all modern diagnostic facilities are still made in a high proportion of cases. Between 1931 and 1944 I performed 84 necropsies on cases of pulmonary carcinoma all in a major general hospital, of these 35 (42 per cent) had been misdiagnosed 19 as some other kind of malignant disease and 16 as non neoplastic diseases. Clearly then the mortality statistics of lung cancer are of dubious value.

(b) Pathological misdiagnoses are still made in not a few cases, and until the last two decades they were very common. Let anyone who doubts this look up some of the standard pathological journals for the later decades of the nineteenth century and study the many records of mediastinal sarcoma lymphadenoma pleural or pericardial endothelioma etc. In the light of what we now know of the structure spread and misleading symptomatology of bronchial

I studied a bronchial adenocarcinoma with metastases in the lungs and lymph glands in a 9-year-old English setter (Fig 160)

POSSIBLE CAUSATIVE FACTORS

Every known inhaled substance and almost every known infection of the lungs has, by one writer or another, been claimed or suggested as a possible factor in the causation of pulmonary carcinoma. The subject is then confused



FIG 160 —Adenocarcinoma of bronchus in a dog ($\times 120$)

and confusing, and there is good reason for a succinct statement separating definitely established facts from a mass of speculation—even at the risk of seeming a little over dogmatic. The whole subject has been well reviewed by Hueper

(1) Infections

(i) *Tuberculosis* has often been described in association with carcinoma (Fried, 1935). In view of the frequency of pulmonary tuberculosis, this of course is inevitable, and no causative relationship can be deduced from such cases. Indeed, Rokitsky's opinion that cancer and tuberculosis were antagonistic has often been cited approvingly. However, there is no evidence to show that phthisis either predisposes to or protects from cancer of the lung.

(ii) *Influenza* was at one time held to predispose to lung cancer, a suggestion which was devoid of any real basis and which now has few supporters.

(iii) *Bronchitis* appears frequently on pension claims as an alleged precursor of cancer, but there is no satisfactory clinical, statistical or pathological evidence to suggest that it predisposes to cancer. 'Bronchitis' is a very popular and very indefinite diagnosis and any chronic lung disease accompanied by a cough

other kinds of carcinoma, the mean age of various series ranging between 45 and 55. The mean age of my 84 necropsy cases was 55, and their age distribution was as follows

Decade	-	-	3rd	4th	5th	6th	7th	8th	9th	Total
No. of cases	-	-	1	5	15	31	22	9	1	84
Percentage	-	-	1	6	18	37	26	11	1	100

The disease is not very uncommon in young people, the ages of my youngest cases were 29, 30 and 33. Field and Quilliam described an anaplastic carcinoma in a girl aged 4 and referred to Hirsch and Ryerson's case of adenocarcinoma in a boy of 5 and to Beardsley's case of adenocarcinoma in an infant of 10 months. Dick and Miller saw a large solitary metastasis in the femur from a bronchial carcinoma in a girl of 9 years.

(3) Sex incidence

All series show a decided preponderance of males with an average of about 80 per cent (Simons). My 84 necropsies comprised 70 men and 14 women, a ratio of 5:1. Since it is very unlikely that there can be any real sexual difference between the lungs of males and females, this striking difference in the sex incidence of lung cancer points strongly to the importance of extrinsic occupational or habitual factors in its causation.

(4) Racial incidence

Pulmonary cancer is recorded from various non-European peoples, e.g. Malays, Chinese, Japanese (Bonne), but of course there are no adequate figures for estimating its real incidence, and comparisons with the white races are not at present possible.

(5) Lung tumours in animals

Mice often develop single or multiple adenomas or adenocarcinomas of the lungs. These tumours first fully described by Tyzzer, have been used extensively in experimental work, as described in Sections I and VI of Chapter 4. In a large number of mice allowed to live their full span of life, Wells *et al.* (1941) found 2 per cent with carcinoma of the lung. Metastases outside the lungs were present in a small proportion of cases, and sarcoma-like structure was seen in many of the tumours. Rats rarely get lung tumours, and areas of bronchiectasis with squamous metaplasia which are common in these animals must not be mistaken for carcinoma. Feldman (1932) mentions infrequent examples of pulmonary carcinoma in the horse, ox, dog, cat, sheep and kangaroo; he himself (1931) described 3 lung tumours in sheep. Apperly described an adenocarcinoma in a fowl. Nieberle and Cohrs (Fig. 158) depicted a large adenoma of a dog's lung, and Poley and Taylor saw a pleomorphic cellular growth accompanied by hypertrophic osteoarthropathy in a young dog. Rudduck and

of such agents, absorption by other routes must also be considered. Tar, oil, soots, tobacco smoke and other smokes, must all be arraigned, but clearly, proof of either the culpability or innocence of any particular material will not be easy to establish. Such proof will entail (a) demonstration of the presence of carcinogenic substances in the suspected material, (b) evidence that the material is inhaled or otherwise absorbed by exposed persons, and (c) evidence that habitually exposed persons do show an excessive incidence of lung cancer, and that this excessive incidence is reduced by eliminating the suspected risk. While the first step (a) has already been accomplished for many of the suspect materials, scarcely any of the evidence (b) or (c) has been obtained, and it will be very difficult to obtain.

For example, suppose that tobacco smoking is an important cause of lung cancer and that it acts by producing chemical carcinogens which are inhaled. It may be easy to identify the carcinogens in tobacco smoke or tar, but it may be difficult to prove that they are effectively inhaled, even more difficult to group patients correctly according to their present and past tobacco consumption, and probably impossible to prevail on any large group of men of homogeneous occupation to renounce smoking for life so that the ultimate incidence of lung cancer in them (proved by necropsy) may be compared with that of their smoking fellows. Comparisons of the smoking habits of victims of lung cancer with those of control cases obtained by careful questionnaires, like Muller's, afford strong grounds for suspecting the carcinogenic results of smoking, but, however strongly suggestive, they cannot afford incontrovertible proof—especially in the eyes of smokers themselves.¹ Proof of the harmfulness of inhaled domestic and industrial soots and smokes or of dust from tarred roads, to which all persons in urban populations are almost equally exposed, will be even more difficult to secure.

(4) Schneeberg and Joachimsthal and radio-active substances

The frequent occurrence of fatal lung disease in the miners of the Erzgebirge has been recognized for over four centuries, but only within recent years has this disease been clearly identified as bronchial carcinoma. Hueper (p. 435) gives a full outline of the subject and Pirchan and Siki's paper (1932) is a valuable source of information. The frequency of lung cancer in workers in the offending mines is very high—about three quarters of the Schneeberg miners and nearly one half of the Joachimsthal miners die of this disease. There is then no doubt of the operation of some highly potent occupational factor, probably an inhaled substance.

The air in the mines contains not only iron, cobalt, nickel and silica dusts, but also arsenic and radio-active substances especially radon. Each of these has been incriminated as the carcinogenic agent by one writer or another, but the weight of the evidence fully outlined by Hueper, points to radon as the main factor. This is supported also by the fact that cancer of the lung has occurred in a number of laboratory workers handling radio-active material. However experimental work has not yet verified the efficacy of inhaled radio-active substances as a cause of lung cancer and until this has been done, a final decision must be deferred.

is apt to be so dubbed until its progress demands a more precise diagnosis. In many cases in which "bronchitis" has appeared to precede the appearance of lung cancer by some months or years the symptoms were caused by the cancer from the beginning. There is no clinical evidence that bronchiectasis predisposes to carcinoma, but Womack and Graham, and Stewart and Allison found minute cancerous foci in bronchiectatic lungs.

(iv) *Pneumonia*—There is no evidence that pneumonia is ever a significant precursor of cancer. Attacks of 'pneumonia' due to bronchial obstruction, or of 'pleurisy' due to the same cause or to tumour invasion of the pleura, are common inaugural symptoms of bronchial carcinoma.

(2) Pneumoconiosis

Hueper gives a full discussion of the contradictory opinions held regarding the possible importance of the several kinds of pneumoconiosis in the causation of lung cancer. *Silicosis* is, of course sometimes seen in association with cancer, and has been thought by some workers (e.g. Klotz) to predispose to this disease, but the evidence is inconclusive, and study of occupational groups exposed to silicosis does not suggest any special predisposition (Vorwald and Karr, Kennaway and Kennaway and other references by Hueper). Experimental results also have been inconclusive. Vorwald and Karr failed to demonstrate any carcinogenic effect of inhaled silicates of various kinds in laboratory animals, but Campbell's experiments (described in Chapter 4) showed an increased incidence of lung tumours in mice following inhalation of inorganic dusts containing silica. *Asbestosis* has been reported in association with carcinoma in a few cases (Holleb and Angrist), and a causative relationship has been suggested because of the youth of several of the patients, predominance of carcinomas of the squamous type, and multicentric origin apparently related to pre-cancerous squamous metaplasia in some of them. However the number of cases is yet too small to permit any definite conclusion to be drawn. *Siderosis* accompanying lung cancer has been described in only a few cases, but the apparently excessive liability of metal grinders to pulmonary carcinoma and the results of Campbell's experiments with dusts containing iron oxide suggest a possible causative relationship. *Anthracosis* has not been proved to be a causative factor. According to Kennaway and Kennaway the registered deaths from lung cancer are fewer in coal miners than in the population generally. It has been suggested however that inhaled atmospheric soot the main source of the common anthracosis of city dwellers may be carcinogenic not because of its carbon content, but because it may contain carcinogenic hydrocarbons, a possibility now to be briefly discussed.

(3) Carcinogenic hydrocarbons

Experimental investigation outlined in Chapter 4 has shown that the incidence of lung tumours in mice can be markedly increased by the administration of carcinogenic hydrocarbons by inhalation or by subcutaneous intraperitoneal or intravenous injections. The possibility must then be conceded that exposure of human beings to such substances may be a factor in the causation of lung cancer and that while inhalation is clearly the most likely mode of introduction

pathological and experimental research. There are strong grounds for believing that inhaled radio active substances can cause lung cancer, but experimental verification of this has yet to be made. Further study is required also on the possible carcinogenic properties of inhaled arsenic, chromates and nickel compounds. Neither trauma nor heredity plays any significant part in human lung cancer.

SITE OF ORIGIN

(1) Side affected

As might be anticipated from the relative sizes of the two lungs, carcinoma of the lung occurs slightly more frequently on the right side than on the left. Of 2,177 cases collected by Simons, the right lung was affected in 1,147, the left in 992, and both lungs in 38 cases. In my 84 necropsy cases, the origins of the tumours were in the right lung in 45 cases, in the left lung in 36, at the bifurcation of the trachea in 2 cases, and diffusely in both lungs in 1 case.

(2) Lobe affected

The lobar distribution of 649 tumours tabulated by Simons was: right upper 169, right middle 70, right lower 119, left upper 179, left lower 112. My corresponding figures were 9, 3, 8, 9, 6, giving closely similar proportions. In many cases, of course, the tumours arise not in particular lobes, but in the main right or left bronchus or at the tracheal bifurcation, this applied to 42 of my 84 cases, and to 179 of Kikuth's 246 cases.

(3) Part of lung affected

At least three quarters of the tumours demonstrably arise in the large bronchus, either the main bronchus or the lobar bronchus in or near the hilar region. In my series the tumours arose in the main bronchus or tracheal bifurcation in 42 cases, in main lobar bronchus in 27 cases, in the periphery of the lung in 6 cases, diffusely and without recognizable local origin in 4 cases, while in 5 cases the tumours were so large that their origin could not be specified. Thus 69 tumours (82 per cent) demonstrably arose from large bronchus. Since the more peripheral tumours do not differ in structure or behaviour from those of obviously bronchial origin it is clear that all or nearly all pulmonary carcinomas are bronchial carcinomas. I have not seen a tumour, or a report of one, for which it seemed necessary to postulate an alveolar origin, and, if such tumours do exist, I see no reason to suppose that they would differ in any special way from other pulmonary carcinomas.

(4) Apical carcinomas

These have been singled out for special description by clinicians, because of their proneness to involve the brachial and cervical sympathetic nerves (Pancoast, Owen *et al*). Pancoast's suggestion that these tumours have a special origin from branchial rests is quite baseless, the tumours are merely apical pulmonary carcinomas. Tumours of other kinds in the same region may of course produce similar symptoms.

(5) Arsenic

The carcinogenic properties of arsenic for the skin naturally suggested that it might be the offending component of the dust in the Erzgebirge mines. There is some evidence too that workers with arsenic-containing sheep dips may be predisposed to lung cancer (Merewether), and it has also been suggested that the considerable quantities of arsenic present in tobacco smoke may be a danger in this respect (see annotation *British Medical Journal* 1946 1, 94). Further statistical and experimental investigation is needed however, before it can be concluded that arsenic is a pulmonary carcinogen.

(6) Chromates

Workers exposed to chromate dusts or fumes develop dermatitis, stomatitis, rhinitis and bronchitis. Over 25 cases of pulmonary carcinoma among chromate workers have been reported (references by Hueper, p. 410), but it is uncertain whether the responsible agents are the chromates themselves or some other substance.

(7) Nickel

Nickel workers often develop dermatitis and the volatile compound nickel-carbonyl produces acute poisoning accompanied by pulmonary oedema and haemorrhages. A high proportion of cases of cancer of the nasal passages and of the lungs has occurred in two Welsh nickel refineries (references by Hueper, p. 417).

(8) Trauma

Cases of carcinoma of the lung attributed to a blow on the chest or a penetrating wound are not unusual in insurance or war pension claims. There is no substantial statistical or pathological basis to support these, and when adequate data are available in such cases it is usually clear that the occurrence of injury prior to the onset of the tumour was purely fortuitous.

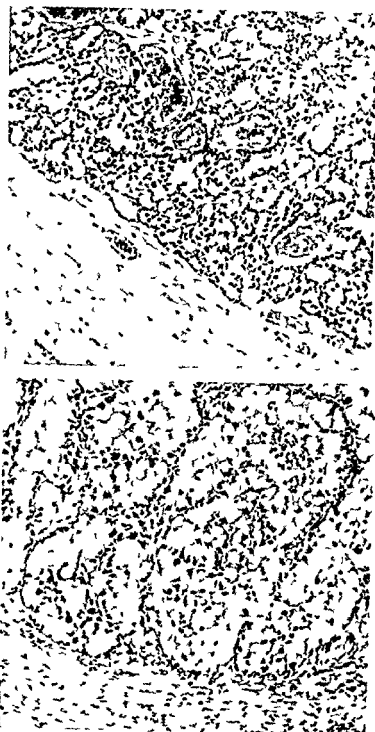
(9) Heredity, and developmental anomalies of the lung

While there is no doubt that different strains of mice differ markedly in the incidence of lung tumours, there is no evidence of any familial predisposition to lung cancer in human beings. Womack and Graham described cases of carcinoma which they believed to have supervened on congenital bronchiectasis or cystic changes, but in my opinion the changes they observed were not developmental but were secondary to the tumours.

(10) Summary of possible causative factors

There is no satisfactory evidence that any of the common infections of the bronchi or lungs predisposes to carcinoma. Silicosis is of doubtful causative importance and the evidence regarding the other forms of pneumoconiosis also is inconclusive. It is quite possible that the inhalation of carcinogenic hydrocarbons or other substances in soots, smokes and dusts, including tobacco smoke, is an important causative factor, but proof of this will entail much more

structure appeared to be present in 65 tumours (77 per cent), while 19 tumours (23 per cent) showed heterogeneous or variable structure. The degree of structural



Figs 162 and 163—Acinar and signet ring cell adenocarcinoma from a woman aged 51, metastases in brain and adrenal respectively ($\times 120$)

range in individual tumours is even greater than that indicated by the foregoing figures for the sections examined were only stray samples of parts of the growths, more thorough examination would certainly have disclosed variable structure in a larger proportion of cases. Figs 161-166 depict some of the main types of structure seen

MICROSCOPICAL STRUCTURE AND ORIGIN

Most writers (e.g. Simons) distinguish at least three main types of pulmonary carcinoma—adenocarcinoma, squamous cell carcinoma and undifferentiated carcinomas—and more elaborate classifications also distinguish oat celled, spheroidal celled, mucoid, papillary and other types of growth. While these names all have descriptive value and while many pulmonary cancers consist predominantly sometimes exclusively of growth of a particular type, it must be emphasized that there is only one entity *carcinoma of the lung*, that individual

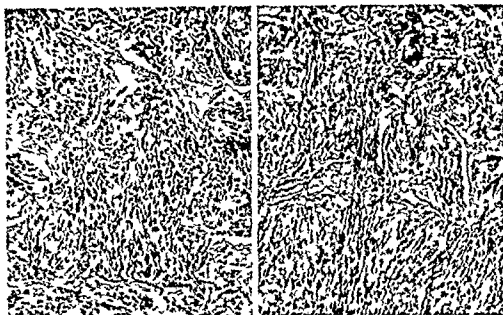


FIG. 161—Spindle-celled carcinoma of bronchus from a man aged 73 ($\times 80$)

tumours show various structural combinations, and that great pleomorphism is possible in one tumour. Review of the microscopical findings in my 84 necropsy cases (an average of 6 sections per case from different parts of the tumours, primary and secondary, were examined) showed the following variations of structure:

Adenocarcinoma only (including acinar, papillary, mucoid and signet ring structure)	-	-	-	-	16 cases
Squamous carcinoma only	-	-	-	-	12 "
Combined squamous and adenocarcinoma	-	-	-	-	2 "
Anaplastic carcinoma only (including oat celled, spindle celled, spheroidal-celled and pleomorphic celled)	-	-	-	-	37 "
Combined anaplastic and adenocarcinoma	-	-	-	-	8 "
Combined anaplastic and squamous carcinoma	-	-	-	-	5 "
Combined anaplastic, squamous and adenocarcinoma	-	-	-	-	4 "

Thus anaplastic or undifferentiated structure was the most common. It was present either alone or along with recognizably differentiated structures, in 54 tumours (64 per cent). Glandular structure alone or in combination was present in 30 tumours (36 per cent). Squamous structure was the least frequent, it was present alone or in combination in 23 tumours (27 per cent). Homogeneous

adenocarcinomas arising from peripheral bronchioles—is absurd Halpert and Pearson's view that all carcinomas of the lung arise from undifferentiated



FIG 165 —Metastasis of mucoid adenocarcinoma in brain from a woman aged 29 A=general structure B=detail including two mitoses ($\times 80$ and 375)

Oat-celled ' or spindle-celled structure (Barnard, Bonser Simpson Karsner and Saphir) is common in bronchial carcinoma. It may form the whole or a large part of the tumour, or it may be found along with squamous-cell or glandular structures. The view adopted by some American writers that oat cell carcinoma is essentially squamous celled is unacceptable, it is anaplastic bronchial carcinoma, and is no more allied to squamous than to glandular epithelium.



FIG 164—From same case as Figs 162 and 163, showing signet ring-cell structure in a metastasis in thyroid gland ($\times 120$)

Certain other opinions regarding the structure and origin of lung cancers must be mentioned here to be deprecated. There has been much discussion as to whether these growths arise usually from the surface epithelium of the bronchi from the bronchial glands or from bronchioles or alveoli with attempts to interpret particular kinds of structure as denoting an origin from one or another of these sources. The pleomorphism of structure of many of the tumours shows plainly however that particular structural variants do *not* denote different specific origins. It is probable that all of the epithelial elements in the fields of origin of the tumours surface epithelia and glands alike participate in their formation just as cancerous change in the breast often affects large and small ducts and acini simultaneously or successively. Extensive origin is particularly apparent in those cases of diffuse lung cancer sometimes bilateral with no distinct single focus in any of the affected bronchi these cases are comparable with diffusely arising breast cancers biliary cancers or leather bottle cancers of the stomach.

Geschickter and Denison's contention that lung cancers are divisible into two groups—hilar epidermoid carcinomas arising from large bronchi and

larger nearly 5 centimetres in diameter in the central part of the left hemisphere. Careful search of all the viscera failed to detect any other growths, but the lungs were saved. Microscopical study of the cerebral growths showed cystic adenocarcinoma of a type strongly suggesting a bronchial origin (Fig 166). The lungs were then thoroughly searched and sections of several doubtful areas in the larger bronchi were prepared but no primary growth was found. Finally, on slicing the lungs into thin slabs a nodule of growth 4 millimetres in diameter was found in the lung substance in the left upper lobe and this consisted of adenocarcinoma resembling that in the cerebral metastases.

(2) Complications of cancer of the lung

These include bronchial occlusion, pulmonary collapse, bronchiectasis, pneumonia and abscess. Infection and cavitation of the tumours themselves sometimes occur (Atkin, Fishberg and Rubin). Pleurisy is frequent, due either to infective complications in the lung, or to cancerous involvement of the pleura, in the latter case commonly producing persistent effusion, often blood stained, and often containing identifiable tumour cells (Figs 48 and 49). Osteo arthropathy is a rare remote effect of pulmonary cancer, but it may be the first symptom of the disease (Craig).

(3) Direct extensions of the growths

These often involve the mediastinum, great veins, pericardium or heart. Gross invasion of the main pulmonary veins in the hilum of the lung is frequent and in some cases the intravenous growths project into the left atrium. Invasion of the superior vena cava or innominate veins is not unusual, and the growth in these veins may extend into the right atrium (Dana and McIntosh). The pulmonary arteries are often compressed or even obliterated by surrounding growth but they are invaded by tumour only rarely (Fig 38). Invasion of the pericardial cavity, usually around the great vessels and base of the heart, may take place directly from the primary growth or from deposits in the mediastinal lymph glands. Epicardial extensions especially in the lymphatics, are not unusual, and they may reach the apex of the heart or may send prolongations into the myocardium. The heart may also suffer direct gross invasion the tumour replacing the myocardium over small or large areas (references, Willis, 1934, p 259). Direct invasion of the oesophagus or of the vertebrae is uncommon. Apical tumours may involve the cervical sympathetic and the brachial plexus.

In many cases one or other of the various complications and extensions enumerated produce the first symptoms of disease, and often lead to errors of diagnosis such as "mediastinal tumour", "pleural tumour", "pericardial tumour", "pleurisy", "pneumonia", "bronchiectasis", "cardiac asthma", "phthisis" etc. In 9 of my 84 necropsy cases, the final clinical diagnosis had been of some non neoplastic intra thoracic disease.

(4) The rate of growth and duration

In Chapter 8 reference was made to Eveleth and Wetzel's case in which following pneumonectomy, a small residue of bronchial carcinoma grew to 2,500 grammes in 58 days, and to a specimen of my own (Case II below) in which a metastasis in the oral mucosa attained a weight of 12 grammes in 4 weeks. On the other hand there occur tumours which lie almost dormant for years, as

'reserve cells' in the bronchial epithelium is devoid of real foundation or meaning, it amounts to a self evident statement that the tumours arise from cells capable of multiplication, and the so called 'reserve cell carcinomas' are merely anaplastic

GROWTH COMPLICATIONS AND LOCAL SPREAD

In their size, rate of growth local spread and production of metastases, pulmonary carcinomas show the utmost diversity. Some tumours attain huge dimensions without producing remote metastases. Others remain small some times almost microscopic yet produce large metastases. Some grow with unexampled rapidity others remain relatively small after several years duration. Some form well defined solid masses of growth others produce more or less uniform diffuse thickening of the walls of the bronchi and others again produce still more diffuse ill defined peribronchial infiltration of wide areas of a lung or of both lungs.



Fig 166—Case 1 Metastasis of adenocarcinoma in brain ($\times 120$)

(1) Minute carcinomas of the lung

These deserve special comment. Womack and Graham described three cases of bronchiectasis in which microscopic foci of abnormal epithelium identical in appearance with undifferentiated carcinoma were found. Stewart and Allison saw a similar focus in a bronchiectatic lung. Turner and I described a case in which a small almost invisible carcinomatous area in a bronchus had produced fatal paraplegia from an extradural secondary growth. In the following case a minute primary growth produced fatal cerebral metastases.

Case 1—A man aged 49 years underwent unsuccessful exploratory operation for cerebral tumour the symptoms of which had appeared recently and progressed rapidly. Necropsy disclosed 2 well-defined partly cystic growths in the cerebrum the

(1) *Extra thoracic lymph glands* are frequently affected, usually by spread from cancerous thoracic glands, but sometimes from metastases in other organs. The most frequently involved are those of the upper abdominal, cervical and axillary groups. Cervical or axillary masses may be the first signs of disease and may cause misdiagnosis, as in a case which I recorded in my 1934 work (p 433, Case 169).

(2) Metastases in serous membranes

The *pleura* of course is frequently involved, dissemination in the pleural cavity has occurred in about one third of necropsy cases, e.g. in 25 of my 84 cases. In some cases, usually those with effusion many nodular metastases are present on both the visceral and parietal pleura in all parts of the cavity, in other cases there are only a few small nodules or plaques of growth at sites other than the region of primary pleural invasion. The *pericardium* is cancerous in about one quarter of fatal cases, and the *peritoneum* in about 10 per cent of cases. Most supposedly primary tumours of the pleura or pericardium are really secondary to undetected bronchial carcinomas (see Chapter 10, and Willis, 1934, p 77, and 1938).

(3) Blood-borne metastases

Metastasis by the blood stream is demonstrable in about three quarters of fatal cases, e.g. in 61 of my 84 cases. The organs most frequently affected are the liver, adrenals, central nervous system, bones, kidneys and lungs themselves but no organ is exempt.

(i) *The liver* contains metastases in nearly one half of fatal cases e.g. in 32, 39 and 47 per cent respectively in Simpson's, Kraft's and my own series. Hepatic enlargement may be the first sign of disease and may lead to a false diagnosis of gastric or other abdominal cancer, as in 3 cases in my 1941 paper.

(ii) *The adrenals* show metastases in a surprisingly high proportion of necropsies, e.g. in 30, 32, 34, 36 and 40 per cent respectively in Simpson's, Bonser's, Kraft's, Glomset's and my series. In most cases these metastases are multiple and bilateral and are usually situated in the medulla. It is not unusual for the adrenals to be the only site of distant metastases, or for the brain and adrenals to be the only sites. Cerebral and adrenal metastases frequently coexist thus applied to 11 of my cases, i.e. to one third of the cases with adrenal deposits and to nearly two thirds of the cases with cerebral deposits. The adrenal growths rarely attain a large size or produce any symptoms.

(iii) *The central nervous system*, usually the brain, contains metastases in about one quarter or one third of fatal cases, e.g. in 31 per cent according to Dosquet, 41 per cent according to Fried and Buckley and 21 per cent in my series. In many cases primary cerebral disease is simulated and a relatively symptomless pulmonary growth is overlooked. Thus, in 11 of Simpson's 19 cases with cerebral metastases, the clinical diagnoses were erroneous, and in 7 of my 18 necropsy cases with metastases in the brain primary cerebral disease had been diagnosed. Elsewhere (1934, p 188) I have referred to many other examples of such misdiagnosis. In all cases diagnosed as "cerebral tumour" and in all cases of cerebral disease of obscure nature, careful radiographic

in my case reported in 1938, in which there was good evidence that a small unsuspected bronchial carcinoma found at necropsy had been present for at least 84 years. Goldman reviewed 11 cases of lung cancer with symptoms for longer than 2 years the durations ranging from 28 to 244 months. 10 of the tumours were of epidermoid type.

While the average symptomatic duration of lung cancer is only a few months this is no guide whatever to the real duration of the tumours. Many of the primary growths remain symptomless and unsuspected during a large part or the whole of their course, and many others are found at necropsy to be of a size and structure clearly showing a duration far longer than that of the symptoms they have produced. In most cases the real duration of lung cancer cannot be determined even approximately and all estimates of average duration based on symptoms are bound to be decided underestimates. This is an important point in considering the alleged causative influence of recent infection or trauma.

(5) Cancer cells in sputum

These have been identified by many workers (references in annotation British Medical Journal 1947: 20) but I believe that the diagnostic reliability of sputum examination has been overestimated. Only a minority of tumours produce free clumps of tumour cells recognizable with certainty, the recognition of isolated tumour cells amongst the various non neoplastic cells in sputum is rarely possible. Diagnosis from sputum examination alone, unverified by biopsy or necropsy should be viewed with great caution.

(6) Simulation of bronchial carcinoma by secondary growths

It is important for both bronchoscopist and pathologist to recognize that secondary growths in the lung sometimes involve the bronchial walls and simulate primary growths in appearance. This may occur from metastatic carcinomas, sarcomas or melanomas (King and Castleman) and I have observed it also from invasion of the main bronchial walls by hilar Hodgkin's disease and lympho sarcoma.

METASTASIS

With no other neoplasm is a knowledge of metastasis more important to the clinician than with pulmonary carcinoma. This tumour metastasizes with great frequency, often widely and often at an early stage while the primary growth is still small and symptomless. More diagnostic mistakes due to metastases are made in this disease than in any other.

(1) Metastases in lymph glands

(i) *The hilar or mediastinal glands* contain tumour deposits in a high proportion of fatal cases e.g. in 104 of Simpson's 139 cases (75 per cent) and in 76 of my 84 cases (94 per cent). These often attain large sizes frequently becoming much bulkier than the primary growth. Infiltrating tumours of the hilum commonly coalesce with the lymph nodal deposits or on the other hand they may incorporate unaffected lymph nodes.

Case II—A man of 70 years had noticed two rapidly growing masses in his mouth for 4 weeks. Examination showed well defined projecting slightly ulcerated purplish masses springing from the gums of the posterior molar regions of the lower jaw one on each side. The larger tumour on the left side was excised, it was an ovoid mass 3 centimetres in main diameter 12 grammes in weight and clothed by stretched partly denuded mucous membrane. Microscopically it showed anaplastic carcinoma suggesting a pulmonary origin and skiagrams revealed a large shadow in the right lower lobe some distance out from the hilum. The remaining gingival metastasis continued to increase rapidly ulcerated and the patient died a few weeks later.

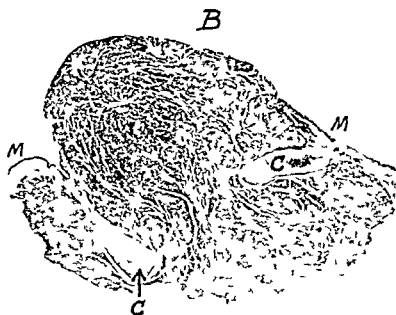


Fig 168—*Case IV* Bronchial adenoma B = lumen of bronchus M = mucosa C = bronchial cartilages enveloped by growth ($\times 6$)

Case III—For 6 months a middle aged man had suffered from an ulcerated growth in the floor of the mouth. This was regarded as a carcinoma and was treated by radium with good result. There then developed a large right sided pleural effusion which was aspirated. The fluid was slightly blood stained and somewhat turbid and mucinous and examination revealed many clumps of tumour cells including signet ring cells distended by droplets of mucin (Fig 48). Skiagrams showed a large mass in the right lung. *Necropsy* revealed a huge mucoid adenocarcinoma replacing most of the right lung with metastases in the thoracic lymph glands, one kidney and both adrenals. There was a scarred area in the floor of the mouth but no residual tumour. It is of course possible that the mouth tumour was an independent primary growth but it seems more probable that it was a metastasis of the lung tumour which must already have been well advanced at the time the oral growth first appeared.

Other unusual metastatic sites included in my series were myocardium, thyroid, pancreas, ovaries, spleen, pituitary gland, mucous membrane of gall bladder, prostate and testis, and references to other examples are given in Chapter 29 of my 1934 work.

BRONCHIAL ADENOMA "

The tumour now commonly designated bronchial 'adenoma' was first described by H. Mueller in 1882. In 1931 Geipel reviewed 6 reported cases.

examination of the lungs should be a routine part of the clinical examination, before any surgical intervention is contemplated. Adherence to this practice would obviate many useless operations.

The metastases of pulmonary carcinoma have a distribution similar to that of metastatic growths in general in the nervous system (1934, pp 353-5 and 366-9)

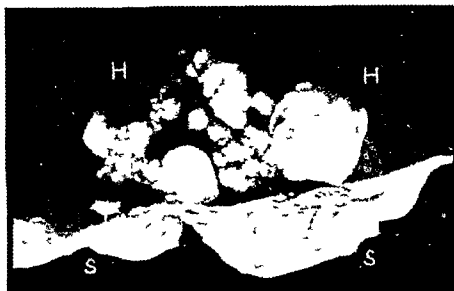


FIG 167—Masses of metastatic growth projecting into hydrocele cavity (HH) from the sac wall (SS) (Slightly reduced)

The metastases are more often multiple than single, are situated about equally often on the two sides and affect the cerebrum, cerebellum, brain stem and spinal cord in that order of frequency. Diffuse or nodular dissemination in the leptomeninges is usually secondary to metastatic deposits in the brain or choroid plexus, as in cases described by Ginsberg, Putscnar, Fried and Shennan, but it is possible that in occasional cases the meninges may be infected by direct spread from the thorax into the theca, as suggested by Rehn, Miller and Alpers and Smith. Massive extradural extensions through the intervertebral foramina may also produce compression of the thoracic part of the spinal cord (Turner and Willis). The papers of Elkington, Minkowski, Globus and Meltzer and Baker contain instructive examples of metastatic tumours of the brain from pulmonary carcinoma.

(ii) *Skeletal metastases* are present in about one-quarter of fatal cases and have often been mistaken for primary tumours or other bone diseases (references 1934 p 189 and Case 136 p 433). Cosin described a man of 25 in whom metastases in many bones from an oat-cell carcinoma produced punched-out areas radiographically resembling myelomatosis, accompanied by anaemia, thrombocytopenia and splenomegaly.

(i) *Other sites* metastases in which have caused difficulties of diagnosis or have caused early symptoms include the eyes (Hudson), the skin (see Case No 263 1934 p 433), intestines (Barnard and Elliott), a hydrocele sac (Willis, 1938 and Fig 167), the tongue (Fitzwilliams) and the oral mucosa as in the following two cases:

post operative haemorrhage into the pleural cavity *Operation Specimen*—A lobulated well defined firm white growth 5 centimetres in main diameter projected into the greatly dilated lobar bronchus and also into the surrounding tissues it had been cut across in its proximal

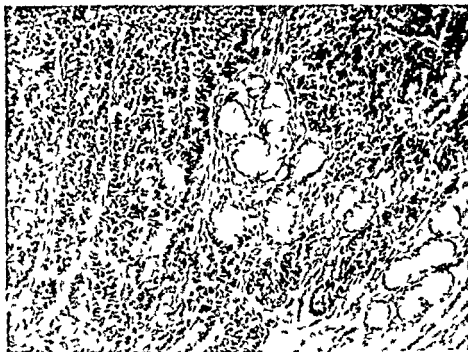


FIG 170 —Case IV Mucous glands included in bronchial adenoma ($\times 120$)



FIG 171 —Case V Bronchial adenoma ($\times 120$)

part where it had involved the main bronchus. The rest of the lung showed bronchiectasis collapse and infection. *Histology* (Fig 171)—Uniform solid trabecular structure but with some glandular acini slight marginal infiltration of surrounding tissues present in

added 2 typical examples, and proposed to distinguish them from the usual bronchial carcinomas by calling them "benign basal-cell carcinomas." Increasing recognition of the tumours and of their favourable outlook following adequate surgical removal led to their separation as a distinct group. Hamperl's description of 9 cases (1937) includes some excellent photomicrographs, and Foster Carter's admirable review of 70 cases (1941) is the best general account.

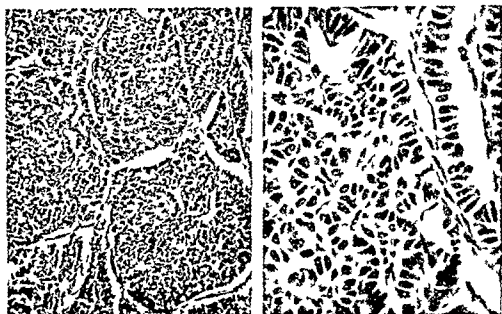


FIG 169—Case IV. Bronchial adenoma: details of structure ($\times 100$ and 400)

(1) Personally studied specimens

I have studied 6 examples of these tumours, all from young adults between the ages of 18 and 40 years, all with long histories from 2 to 16 years in duration, and all with characteristic gross and microscopic structure (Figs 168-175). I record the following three examples.

Case IV—History—Right lower lobectomy successfully performed by Mr C J O Brown of Melbourne on a man aged 40 years, following a history of cough and haemoptysis for 2 years. *Gross Structure*—Main lower lobe bronchus the site of a well-defined white tumour 3 centimetres in diameter projecting into the bronchus and also expanding into the surrounding lung tissue, with bronchial cartilages visibly included in the tumour (Fig 168). Remainder of lobe shows obstructive bronchiectasis, collapse and infection. *Histology* (Figs 169 and 170)—Uniform structure of solid epithelial masses and trabeculae, but with formation of distinct glandular tubules in places. Distinct infiltration of the bronchial mucosa and of the extra-bronchial tissues present at parts of the growth margins. Some of the bronchial mucous glands included within the tumour show apparent direct transition from glands to tumour (Fig 170). Some markedly enlarged hilar lymph glands showed inflammatory changes only.

Case I—History—A woman aged 39 years had had attacks of pneumonia at the ages of 7 and 16, and since the age of 23 (i.e. for 16 years) had had frequent haemoptyses. Tuberculosis had been suspected, but bacilli were not found and her general health remained good. Investigation disclosed a growth in the right lower lobe bronchus and Mr C J O Brown performed lobectomy with difficulty. Death occurred from

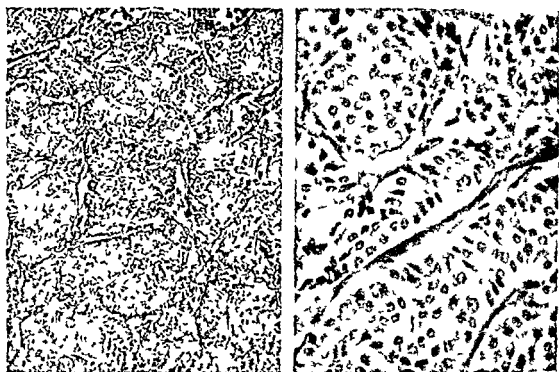


FIG 173 —Bronchial adenoma from a man aged 28 solid trabecular structure ($\times 100$ and 400)

(ii) *Age incidence* —The tumours develop much earlier in life than most bronchial carcinomas. In those reviewed by Foster Carter, the mean age of onset of symptoms was 28, 70 per cent had given symptoms in the third and fourth decades, and the age range was 11 to 66 years. The symptomatic duration was often very long, the average duration prior to diagnosis being about 5 years, the longest recorded duration being 40 years and in Foster Carter's own series 23 years. In my Case V, the tumour had certainly been present for 16 and possibly 32 years. In some of the recorded cases the tumour has been observed to remain stationary for several years.

(iii) *Sex incidence* —Unlike carcinoma bronchial "adenoma" affects the sexes about equally, 62 per cent of the patients reviewed by Foster Carter were females.

(iv) *Site* —Bronchial "adenoma" is invariably situated in a large bronchus close to the hilum, never in the periphery of the lung. Right sided tumours are more frequent than left sided, and the favourite situation is in the right lower lobe bronchus.

(v) *Causative factors* —These are unknown. The equal sex liability suggests that the occupational factors which certainly play a part in the causation of bronchial carcinoma are not important as regards "adenoma", and Foster Carter's patients had no distinctive occupations.

(3) Structure and growth

(a) Gross appearance

The tumours are well defined, firm uniform rounded or lobulated masses, averaging 3 or 4 centimetres in diameter, projecting into the bronchial lumen.

places stroma contains scattered spicules of bone. Enlarged bronchial lymph glands clear of growth. Necropsy showed a small part of the growth left in the main bronchus but no metastases.



FIG 172—Case VI Tumour of trachea ($\times 120$)

Case VI—History—A woman of 24 years had had several haemoptyses during the previous 3 years, 1 year of which she spent in a tuberculosis sanatorium. Repeated sputum examinations showed no bacilli and skiagrams of lungs showed no abnormalities. Bronchoscopy showed a soft readily bleeding mass of growth partly occupying the trachea at the level of the manubrium. *Histology* (Fig 172)—Pieces of this growth showed well-differentiated branching glandular tubules solid epithelial cords and cribriform clumps resembling those often present in salivary tumours set in plentiful vascular partly hyalinized stroma. Many of the glandular components of the growth were in gentle continuity with glands of the tracheal mucosa. *Later Progress*—Deep X ray therapy was instituted but 6 months later the patient had lost condition pain and weakness of the left arm had developed and a small subcutaneous nodule had appeared on the back. This was excised and showed an active carcinomatous growth composed mainly of large clumps of anaplastic epithelium with many mitoses but with areas of narrow trabecular structure resembling that of the tracheal tumour. Small patches of bone were present in the stroma. Skiagrams showed partial destruction and collapse of the first dorsal vertebra. The patient died a month later. *Necropsy*—A mass of growth springing from the posterior wall nearly filled the trachea from about 5 centimetres below the glottis to just above the bifurcation. Multiple metastatic growths were present in both lungs pleura mediastinal lymph glands liver and vertebrae. Microscopically these generally resembled the subcutaneous metastasis.

(2) Incidence and causation

(i) *Frequency*—Bronchial adenomas appear to constitute about 5 per cent of bronchial tumours. My 6 specimens came under observation during the same period in which my 84 necropsies on cases of bronchial carcinoma were performed.

"adenomas" as well as the salivary tumours arise specifically from "onkocytes". Nor is there any substantial evidence to sustain Womack and Graham's opinion

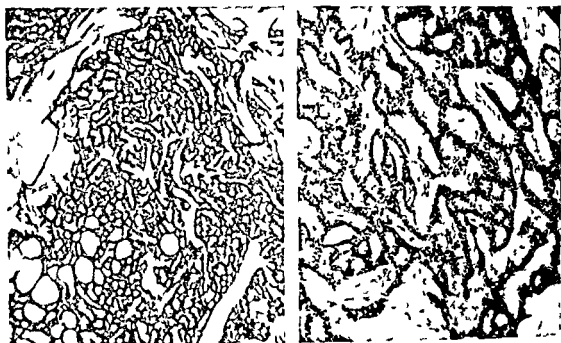


FIG 175—Bronchial adenoma from a man aged 32 retiform trabecular structure ($\times 50$ and 120)

that they are "mixed" tumours of developmental origin, the occasional presence of bone or cartilage in them is readily attributable to metaplasia or to the inclusion of parts of bronchial cartilages

(d) Malignancy

The tumours grow mainly expansively, but restricted infiltration of the submucous tissues or lung is often to be seen at their margins. It is usually stated that metastasis does not occur, but Adams *et al* have reported metastasizing growths not sharply separable from the "adenomas", and my Case VI is a striking instance of the same kind. Hence, while admitting that the name "adenoma" is justified by the frequently benign behaviour of the tumours, we must be prepared to see occasional members of the group transgress the bounds of innocence, just as with the pleomorphic salivary growths. The prevalent opinion that the group is sharply distinct from carcinoma and invariably benign is unjustified.

OTHER BENIGN EPITHELIAL TUMOURS

After segregation of the distinctive group of bronchial "adenomas", there is left a rather miscellaneous assortment of rare benign bronchial and pulmonary tumours variously recorded as papillomas, "fibro adenomas", "hamartomas", "chondromas", and "mixed tumours". Some examples of these will explain their structure and possible relationships.

The so called "chondromas" of the lung, well described by Moller, and by

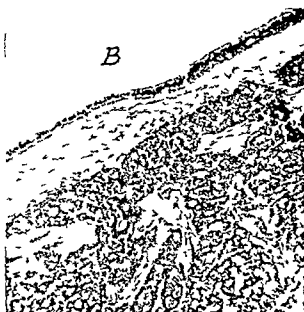


FIG 174 —Bronchial adenoma from a girl aged 18 B = lumen of bronchus note intact mucosa ($\times 80$)

but usually covered by an intact layer of distended mucosa. In many cases the tumour is like an iceberg in that its bulkiest part lies outside the bronchus in the surrounding hilar or lung tissue and its presenting part seen bronchoscopically is its smaller part. Apart from cough and haemoptysis, the main symptoms are those produced by bronchial obstruction with collapse and infection of the lung.

(b) *Microscopic structure*

This differs from tumour to tumour but is usually very uniform throughout each individual tumour. About one third of the specimens show well differentiated glandular acini or tubules usually without but sometimes with mucoid secretion but the remaining two thirds consist mainly of solid epithelial columns or masses with only scattered signs of glandular orientation of the cells. The polyhedral, wedge shaped or elongated cells are uniform in size and structure, without signs of disorderly growth and with only occasional mitotic figures. The vascular fibrous stroma is usually scanty but sometimes more plentiful and hyaline sometimes it contains areas of metaplastic bone as in Womack and Graham's case and 3 of my cases including V and VI above.

(c) *Origin*

There is I think little room for doubt that the tumours arise from the mucous and mixed glands of the bronchial wall and that they are as Foster Carter suggests comparable with the more benign of the pleomorphic salivary tumours. They resemble those tumours in their circumscription, slow growth and variable structure, they differ from them in rarely secreting much mucus and in their more regular benignity. My Cases IV and VI showed evidence of direct continuity of the growth with the mucosal glands. I see nothing to favour the view, suggested by Hamperl and supported by Stout that the bronchial

intra canalicular fibro adenomas of the breast, but their stroma consisted in one case of fibrous and adipose tissue and in the other of fibrous tissue only and was devoid of cartilage. Had their stroma chondrified, their structure would have been identical with that of the "chondromas."

Harris and Schattenberg reported two peculiar "anlagen tumours" in the lungs of new born infants. In one case an entire lobe was replaced by a mass consisting of branching tubules lined by columnar cells, and separated by scanty stroma containing islands of cartilage. In the other case the left upper lobe contained an irregular vascular mass with the structure of embryonic lung tissue. Whether these masses were true tumours, is, I think doubtful, they were probably developmental anomalies without powers of independent growth.

In the lungs of a woman aged 73, Richardson found multiple small nodules composed of glandular structures lined by mucoid columnar epithelium. No primary tumour was found elsewhere, and the condition was diagnosed as multifocal "adenomatosis" of the lung.

REFERENCES

- Adams W E Steiner, P E and Bloch R G (1942) *Surgery* 11, 503
 Alpers B J and Smith O N (1938) *Amer J Cancer*, 32 361
 Apperly F L (1935) *Amer J Cancer* 23 556
 Atkin E E (1931) *J Path Bact* 34 343
 Baker A B (1942) *Arch Path* 34 495
 Barnard W G (1926) *J Path Bact* 29 241
 Barnard W G and Elliott T R (1930) *Quart J Med* 23 407
 Bonne C (1936) *Internat Congress against Cancer* 1 492
 Bonser G M (1928 and 1934) *J Hyg* 1928, 28 340 1934, 34, 218
 Bonser G M (1934) *J Path Bact* 38 209
 Cosin L (1935) *Brit J Surg* 23 110
 Craig J W (1937) *Brit Med J*, 1 750
 Dana, H W and McIntosh R (1922) *Amer J Med Sci* 163 411
 Davidson M (1930) *Cancer of the Lung*, Bristol
 Dick A and Miller H (1946) *Brit Med J* 1 387
 Dosquet (1921) *Virchows Arch* 234 481
 Duguid, J B (1927) *Lancet* 11 111
 Elkington J S (1935) *Proc Roy Soc Med* 28 1080
 Eveleth M S and Wetzel N C (1941) *Cancer Res* 1 721
 Feldman W H (1931) *Amer J Cancer* 15 2044
 Feldman W H (1932) *Neoplasms of Domesticated Animals* Philadelphia
 Field C E and Quilliam J P (1943) *Brit Med J* 1 691
 Fishberg M and Rubin E H (1929) *Amer J Med Sci* 178 20
 Fitzwilliams D C L (1938) *Proc Roy Soc Med* 31 551

Goldsworthy, are not simple chondromas but always contain bronchial epithelium in clefts between the cartilaginous masses and may include also mucoid, adipose,



FIG 176—Case *II* Chondroma of lung E = epithelial clefts C = chondrification in fibrous tissue F = fat cells in fibro-cartilaginous tissue ($\times 80$)

fibrous lymphoid and muscular tissue Möller who for this reason called them mixed tumours described a typical specimen from a man aged 44 and showed that the structure was exactly comparable with that of an intra canicular fibro adenoma of the breast consisting of a papillary growth of the bronchial epithelium with bulky overgrowth of the stroma Möller supposed that cartilage formation in the stroma was brought about by a specific inductive effect of the proliferating epithelium on the connective tissue Goldsworthy observed similar structural relationships in a specimen from a man aged 58 which he designated hamartoma chondromatosum However I think it unnecessary to postulate any developmental anomaly as the origin of these tumours the structure of which can readily be accounted for in the way suggested by Möller A personally studied specimen may be briefly described

Case III—At necropsy on a man of 66 years who died of carcinoma of the colon an incidental finding was a solitary well defined firm nodule 1 centimetre in diameter situated in the middle of the lower lobe of the left lung This was at first thought to be a metastatic growth with some mucoid change but microscopical study showed it to consist of irregular masses of fibro-cartilage mingled with some adipose tissue partly separated by clefts lined by cubical or columnar epithelium which was ciliated in places (Fig 176) Much of the stroma was fibroblastic and all transitions from fibrous tissue to cartilage could be traced

The two fibro adenomas of the lung described by Scarff and Gowar were probably related to the chondromas These tumours found in men 24 and 66 years old respectively, also showed a structure like that of the

intra canalicular fibro adenomas of the breast, but their stroma consisted in one case of fibrous and adipose tissue and in the other of fibrous tissue only and was devoid of cartilage. Had their stroma chondrified, their structure would have been identical with that of the "chondromas".

Harris and Schattenberg reported two peculiar 'anlagen tumours' in the lungs of new born infants. In one case an entire lobe was replaced by a mass consisting of branching tubules lined by columnar cells, and separated by scanty stroma containing islands of cartilage. In the other case the left upper lobe contained an irregular vascular mass with the structure of embryonic lung tissue. Whether these masses were true tumours, is, I think, doubtful, they were probably developmental anomalies without powers of independent growth.

In the lungs of a woman aged 73, Richardson found multiple small nodules composed of glandular structures lined by mucoid columnar epithelium. No primary tumour was found elsewhere, and the condition was diagnosed as multi focal 'adenomatosis' of the lung.

REFERENCES

- Adams W E Steiner P E, and Bloch R G (1942) *Surgery* 11 503
 Alpers B J and Smith O N (1938) *Amer J Cancer* 32 361
 Apperly F L (1935) *Amer J Cancer* 23 556
 Atkin E E (1931) *J Path Bact* 34 343
 Baker A B (1942) *Arch Path* 34 495
 Barnard W G (1926) *J Path Bact* 29 241
 Barnard W G and Elliott T R (1930) *Quart J Med* 23 407
 Bonne C (1936) *Internat Congress against Cancer* 1 492
 Bonser G M (1928 and 1934) *J Hyg* 1928 28 340 1934, 34, 218
 Bonser G M (1934) *J Path Bact* 38 209
 Cosin, L (1935) *Brit J Surg* 23 110
 Craig J W (1937) *Brit Med J* 1 750
 Dana, H W and McIntosh R (1922) *Amer J Med Sci* 163 411
 Davidson M (1930) *Cancer of the Lung* Bristol
 Dick A and Miller H (1946) *Brit Med J* 1 387
 Dosquet (1921) *Virchows Arch* 234 481
 Duguid J B (1927) *Lancet* ii 111
 Elkington J S (1935) *Proc Roy Soc Med* 28 1080
 Eveleth M S and Wetzel N C (1941) *Cancer Res* 1 721
 Feldman W H (1931) *Amer J Cancer* 15 2044
 Feldman W H (1932) *Neoplasms of Domesticated Animals* Philadelphia
 Field C E and Quilliam J P (1943) *Brit Med J* 1 691
 Fishberg M and Rubin E H (1929) *Amer J Med Sci* 178 20
 Fitzwilliams D C L (1938) *Proc Roy Soc Med* 31 551

- FOSTER CARTER A T (1941) Bronchial adenoma *Quart J Med* 10 139 (An excellent review)
- Fried B M (1925 and 1927) *Arch Int Med* 1925 35 1 1927 40 340
- Fried B M (1935) *Amer J Cancer* 23 247
- FRID, B M, and BUCKLEY R C (1930) Primary carcinoma of the lungs Intracranial metastases *Arch Path* 9 483
- FRISSELL L F and KNOX, L C (1937) Primary carcinoma of the lung *Amer J Cancer* 30 219 (A valuable well illustrated general account)
- Geipel P (1931) *Frankfurt Z Path* 42 516
- Geschickter C F and Denison R (1934) *Amer J Cancer* 22 854
- Ginsberg S (1921) *Klin Mbl Augenheilk* 67 232
- Globus J H and Meltzer T (1942) *Arch Neurol Psych* 48 163
- Glomset D A (1938) *Amer J Path* 32 57
- Goldman A (1942) *J Amer Med Assoc* 118 359
- Goldsworthy N I (1934) *J Path Bact* 39 291
- Halpert B and Pearson B (1940) *Amer J Cancer* 40 213
- Hamperl H (1937) *Virchows Arch* 300 46
- Harris W H and Schattenberg H J (1942) *Amer J Path* 18 955
- Holleb H B and Angrist A (1942) *Amer J Path* 18 123
- Hudson A C (1934) *Proc Roy Soc Med* 27 304
- Hueper W C (1942) *Occupational Tumors* Springfield
- Karsner H T and Saphir O (1930) *Amer J Path* 6 553
- KENNAWAY N M and KENNAWAY E L (1936) Study of the incidence of cancer of the lung and larynx *J Hyg* 36 236 (An interesting discussion of possible occupational and atmospheric factors in causation)
- KIKUTH W (1925) Über Lungencarcinom, *Virchows Arch* 255 107 (A good account of 246 necropsies)
- King D S and Castleman B (1943) *J Thor Surg* 12 305
- Klotz M O (1939) *Amer J Cancer* 35 38
- KRAFT J A (1934) Pathologische Anatomie und Histologie des primären Lungenkrebses *Z Krebsforsch* 41 51 (A careful study of 150 cases)
- Maxwell J (1930) *J Path Bact* 33 233
- Merewether E R A (1943) *Ann Rep Chief Inspector of Factories for 1943* p 38
- Miller J W (1917) *Zbl allgem Path* 28 161
- MINKOWSKI M (1941) Über metastatische Hirngeschwülste *Schweiz. Arch Neurol Psych* 47 Part 9
- MOLIER A (1933) Zur Entstehung der Lungenmischgeschwülste *Virchows Arch* 291 478 (An excellent study of the so-called chondroma)
- Muller F H (1939) *Z Krebsforsch* 49 57
- Nieberle K and Cohrs P (1931) *Lehrbuch der Spec. Path Anat der Haustiere* Jena
- Owen D Hewer T F and Whitaker P H (1938) *Brit Med J* ii 1360
- Pancoast, H K (1932) *J Amer Med Assoc* 99 1391
- PASSEY R D and HOLMES J M (1935) The incidence of intrathoracic neoplasia in the teaching hospitals of Great Britain *Quart J Med* 4 321
- PIRCHAN A and SIKL, H (1932) Cancer of the lung in the miners of Jackymov *Amer J Cancer* 16 681 (An excellent account)
- Poley P P and Taylor J S (1942) *J Amer Vet Med Assoc* 100 346
- Putschar W (1930) *Altn Wschr* 9 1699
- Rehn F (1906) *Virchows Arch* 186 307
- Richardson G O (1943) *J Path Bact* 51 297
- Scarff R W and Gower I J S (1944) *J Path Bact* 56 257
- Shennan T (1928) *J Path Bact* 31 365
- Simons F J (1937) *Primary Carcinoma of the Lung* Chicago
- SIMISON S L (1929) Primary carcinoma of the lung *Quart J Med* 22 413 (A good account of 139 necropsies)
- Sitsen A F (1935) *Z Krebsforsch* 42 30
- Steiner P E (1944) *Arch Path* 37 185
- Stewart M J and Allison P R (1943) *J Path Bact* 55 105
- Stout A I (1943) *Arch Path* 35 803

- Turner E K and Willis R A (1938) *Med J Austral*, **11** 866
 Vorwald A J and Karr J W (1938) *Amer J Path*, **14** 49
 Wahl S (1927) *Z Krebsforsch* **25** 302
 Wells H G Slye M and Holmes H F (1941) *Cancer Res* **1** 259
 Willis R A (1934) *The Spread of Tumours in the Human Body* London
 Willis R A (1941) *Med J Austral* **11** 258
 Willis R A (1938) *J Path Bact* **47** 35
 Womack, N A and Graham E A (1938 and 1942) *Arch Path* 1938 **26** 165 1942, **34** 301
 Womack N A, and Graham, E A (1941) *Amer J Path*, **17** 645

- FOSTER CARTER A F (1941) Bronchial adenoma *Quart J Med* 10 139 (An excellent review)
- Fried B M (1925 and 1927) *Arch Int Med* 1925 35 1 1927, 40 340
- Fried B M (1935) *Amer J Cancer* 23 247
- FRID B M and BUCKLEY R C (1930) Primary carcinoma of the lungs Intracranial metastases *Arch Path* 9 483
- FRISSELL L F and KNOX L C (1937) Primary carcinoma of the lung *Amer J Cancer* 30 219 (A valuable well illustrated general account)
- Geipel P (1931) *Frankfurt Z Path* 42 516
- Geschickter C F and Denison R (1934) *Amer J Cancer* 22 854
- Ginsberg S (1921) *Klin Mbl Augenheilk* 67 232
- Globus J H and Meltzer T (1942) *Arch Neurol Psychiat* 48 163
- Glomset D A (1938) *Amer J Path* 32 57
- Goldman A (1942) *J Amer Med Assoc* 118 359
- Goldsworthy N E (1934) *J Path Bact* 39 291
- Halpert B and Pearson B (1940) *Amer J Cancer* 40 213
- Hamper H (1937) *Virchows Arch* 300 46
- Harris W H and Schattenberg H J (1942) *Amer J Path* 18 955
- Holleb H B and Angrist A (1942) *Amer J Path* 18 123
- Hudson A C (1934) *Proc Roy Soc Med* 27 304
- Hueper W C (1942) *Occupational Tumors* Springfield
- Karsner H T and Saphir O (1930) *Amer J Path* 6 553
- KENNAWAY N M and KENNAWAY E L (1936) Study of the incidence of cancer of the lung and larynx *J Hyg* 36 236 (An interesting discussion of possible occupational and atmospheric factors in causation)
- KIKUTH W (1925) Über Lungencarcinom *Virchows Arch* 255 107 (A good account of 246 necropsies)
- King D S and Castleman B (1943) *J Thor Surg* 12 305
- Klotz M O (1939) *Amer J Cancer* 35 38
- KRAIT I A (1934) Pathologische Anatomie und Histologie des primären Lungenkrebses *Z Krebsforsch* 41 51 (A careful study of 150 cases)
- Maxwell J (1930) *J Path Bact* 33 233
- Merewether E R A (1943) *Ann Rep Chief Inspector of Factories for 1943* p 38
- Miller J W (1937) *Zbl allgem Path* 28 161
- MINKOWSKI M (1941) Über metastatische Hirngeschwülste *Schweiz Arch Neurol Psychiat* 47 Part 9
- MOLLER A (1933) Zur Entstehung der Lungenmischgeschwülste *Virchows Arch* 291 478 (An excellent study of the so-called chondroma)
- Müller F H (1939) *Z Krebsforsch* 49 57
- Nieberle K and Cohrs P (1931) *Lehrbuch der Spec. Path Anat der Haustiere* Jena
- Owen D Hewer T F and Whitaker P H (1935) *Brit Med J* ii 1360
- Pancoast H K (1932) *J Amer Med Assoc* 99 1391
- PASSFY R D and HOLMES J M (1935) The incidence of intrathoracic neoplasia in the teaching hospitals of Great Britain *Quart J Med* 4 321
- PIRCHIAN A. and SIKL, H (1932) Cancer of the lung in the miners of Jackmoyv *Amer J Cancer* 16 681 (An excellent account)
- Poley P P and Taylor J S (1942) *J Amer Vet Med Assoc* 100 346
- Putsch W (1930) *Klin Wschr* 9 1699
- Rehn E. (1906) *Virchows Arch* 186 307
- Richardson G O (1942) *J Path Bact* 51 297
- Scarff R W and Gower F J S (1944) *J Path Bact* 56 257
- Shennan T (1928) *J Path Bact* 31 365
- Simons, C J (1937) *Primary Carcinoma of the Lung* Chicago
- SIMPSON S L. (1929) "Primary carcinoma of the lung" *Quart J Med* 22 413 (A good account of 139 necropsies)
- Sitsen A E (1935) *Z Krebsforsch* 42 30
- Steiner P E (1944) *Arch Path* 37 185
- Stewart M J and Allison P R (1943) *J Path Bact* 55 105
- Stout A P (1943) *Arch Path* 35 803

cases Souttar's oesophagoscopy examination of 98 cases showed the upper limits of the growths to be in the upper third (less than 10 inches from the teeth) in 16 cases, in the middle third (10 to 14 inches from teeth) in 69 cases, and in the lower third (15 inches or more from teeth) in 13 cases. The upper limits of 436 growths in the Cancer Campaign series were—upper part 52, middle part 204, lower part 180. At necropsy many of the tumours are so extensive that their precise level of origin is uncertain. A prevalent idea that the narrow regions of the oesophagus are thereby predisposed to cancer is very dubious.

CAUSATIVE FACTORS

Although it is very probable that dietetic and dental factors—alcohol, tobacco, insufficient mastication, hot foods, foods containing chemical carcinogens, or foreign bodies—are largely responsible for cancer of the gullet, it is naturally difficult to prove the culpability of any particular factor. Careful inquiries into the dietetic habits of patients with oesophageal and gastric cancer, like that recorded by Craver, but in much larger series of cases, are needed. The problem is more fully discussed in the next chapter.

Schaer referred to reported cases of oesophageal cancer associated with leucoplakia, diverticula, ulcerative and inflammatory lesions and compression of the organ by aneurysms or bony projections from spondylitis. Schaer himself examined 237 oesophagi for possibly pre-cancerous lesions, he concluded that leucoplakia is very commonly present in the adult organ and cannot be regarded as an important pre-cancerous lesion, that suspicious epithelial proliferation or definite carcinoma is sometimes seen in or near diverticula, and that other inflammatory lesions also may occasionally precede cancer. However, the evidence on these matters seems to me to be inconclusive. The association of leucoplakia with cancer was studied also by Sharp. The Plummer-Vinson syndrome as a precursor of oesophageal cancer (see Ahlbom's findings cited in Chapter 15) probably applies only to post-cricoid cancer, but further investigation is needed.

STRUCTURE

Little need be said of this. With rare exceptions the tumours are *epidermoid carcinomas* resembling those of the oral cavity or pharynx, they vary much in degree of differentiation from highly cornifying tumours to disorderly anaplastic growths devoid of recognizable epidermoid characters. Lympho-epitheliomas do not occur. Tumours of basal cell type are said to occur, but I have never seen an example.

Rare *adenocarcinomas*, sometimes mucoid in type have been reported by Franke and by Kaufmann. Some writers have suggested that these may arise from the small islands of gastric mucosa which are common in the upper part of the oesophagus, but tumours of this origin would not be distinguishable from those arising in the glands of the oesophagus itself.

LOCAL EXTENSION

Many tumours extend annularly and produce stenosis, others spread longitudinally, forming an oval ulcer, plateau or fungus. They soon invade and replace

CHAPTER 20

CARCINOMA OF THE OESOPHAGUS

CARCINOMA is the only common tumour of the oesophagus adenomas and papillomas are very rare Simple submucous cysts lined by squamous stratified epithelium are not uncommon but are seldom large enough to cause symptoms

AGE SEX RACE AND SPECIES INCIDENCE

(1) Age

The age distribution curve of cases of carcinoma of the oesophagus has its peak late in the sixth decade, or in some series in the seventh More than three-quarters of the tumours appear in people over 50 years old The mean age of Pack and Le Fevre's series was 57, and of those in the British Empire Cancer Campaign report (1942) 65 years The mean age at death of my 35 necropsy cases was 67 The disease is rare under 40 years of age but has been seen at 21 and 19 years (Kaufmann, Klein)

(2) Sex

The disease is much commoner in men than in women, the combined figures of Kaufmann, Souttar, Graham and Ballon and my own necropsy cases show that 87 per cent of 471 patients were men a percentage the same as in Klein's series Post cricoid carcinoma, considered in Chapter 15 is much commoner in women

(3) Race

Because of the considerable proportion of diagnostic errors (see Chapter 5), no accurate racial comparisons are possible for oesophageal cancer The disease is common in all European races, and has often been reported in Negroes, Indians, Chinese and other Eastern peoples

(4) Species

Moschikowitz and Sprinz reporting a carcinoma of the oesophagus in an antelope, cited other rare records of this disease in cats, horses, bovines, a primate, a fowl, a mule, a sheep and a turkey

SITE

Reported series show wide differences in the distribution of the tumours Graham and Ballon cited the following range of differences recorded—in the upper third of the organ 12 to 27 per cent of the tumours, in the middle third 30 to 49 per cent, in the lower third 26 to 63 per cent Klein reviewed several reported series which showed the middle third to be the most frequent site The sites in Kaufmann's cases were upper third 31, middle third 61, lower third 84

upper oesophagus may produce bulky cervical tumours as the first or main symptoms as in cases described by Kaufmann, Erdheim, and Davies. Carcinomas of the lower half of the oesophagus frequently produce metastases in the upper abdominal, as well as the mediastinal, lymph glands. Secondary invasion of the stomach from deposits in the glands around its cardiac end may simulate the appearance of an independent primary gastric growth (Borrmann).

(2) Blood borne metastases

These are present in about one-third of fatal cases (Klein, Kaufmann, Willis) the commonest sites being the liver and lungs. In my 2 necropsy cases with cerebral metastases these had very similar situations, in one case there was a single nodule in the left occipital cortex, and in the other case each occipital pole contained a metastatic nodule. In cases recorded by Franke and Souttar, symptomless primary growths had produced multiple cerebral metastases, simulating cerebral tumour.

REFERENCES

- Borrmann, R (1907) *Verh Dtsch path Ges* 11 108
 British Empire Cancer Campaign (1942) *Annual Report*, 19, 65
 Clayton E S (1928) *Surg Gyn Obst* 46 52
 Criver, L F (1932) *Amer J Cancer* 16 68
 Davies H M (1910) *Brit Med J* 1 363
 Erdheim S (1921) *Arch klin Chir* 117 274
 Franke (1903) *Virchows Arch* 174 563
 Geipel P (1899) *Zbl allgem Path* 10 846
 Graham E A, and Ballou H C (1931) *Ann Otol etc* 40 895
 Hebb R G (1898) *Trans Path Soc Lond* 49 32
 KAUFMANN, C (1929) *Pathology*, p 638 (Translation by *Journal of Teucopria*
 the best general accounts of carcinoma of the oesophagus (as in Chapter 15)
 Klein A (1927) *Arch klin Chir* 145 166
 Leichtenstern O (1891) *Dtsch med Wschr* 17 535
 Moschkowitz L and Sprinz H (1940) *Amer J Cancer*, 38
 Pack G T and Le Fevre R G (1930) *J Cancer Res* 14
 Schaer H (1930) *Z Krebsforsch* 31 217
 Sharp G S (1931) *Amer J Cancer* 15, 2029
 Souttar H S (1927) *Brit J Surg* 15 76
 Willis R A (1941) *Med J Austral* 1 258

rs are epidermoid
 ev vary much in
 rderly anaplastic
 pho-epitheliomas
 I have never seen

the muscle coat and the peri oesophageal tissues. Ulceration of soft growths leads to ragged sloughing and suppuration in them. Outcrop satellite growths in the neighbouring oesophageal or gastric mucosa are not unusual, although these may appear to be separate from the main mass. Microscopical study usually shows plainly that they have resulted from submucosal extensions in lymphatics or blood vessels. Occasionally however, multifocal tumour formation appears to have taken place and certainly some early carcinomas show clear evidence of tumour genesis still in progress at their margins (Fig 177).

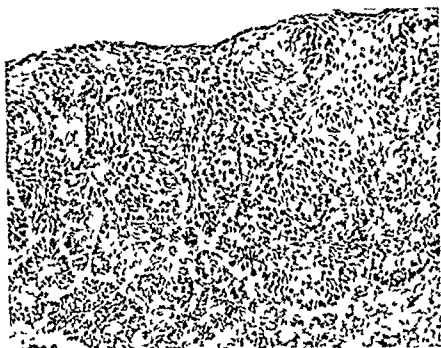


FIG 177 —Epithelium marginal to a large ulcerated carcinoma of oesophagus showing cancerous change *in situ* comparable with Bowen's disease of the skin ($\times 120$)

Invasion or perforation of surrounding organs the lungs bronchi trachea aorta heart pleural cavity or spine is very frequent. Invasion of lungs or bronchi leads to septic pneumonia a common cause of death from oesophageal cancer. Invasive complications may occur from symptomless or unsuspected growths e.g. Kaufmann saw fatal paraplegia from spinal invasion and in one of my necropsy cases an apparently healthy man had died suddenly from perforation of the aorta. Invasion of the pericardium or heart is exemplified by the cases of Hebb and Geipel, the latter saw direct perforation of the growth into the left atrium. Leichtenstern saw invasion of the azygos vein and intravascular growth into the superior vena cava and right chambers of the heart.

METASTASIS

(1) Metastases in lymph glands

These often occur early and are present in over two thirds of necropsy cases (Klein Clayton Willis). Like oral and pharyngeal growths those of the

must have improved diagnosis of recent years, and an apparent trend in the frequency of gastric cancer might be only a trend in the proportion of cases identified as such

(2) Age incidence

In most series the greatest number of cases occurs in the sixth decade Konjetzny gives the mean age as 54 years, which was the same as in Pack and Le Fevre's hospital series. The mean age of Poscharissky's 500 necropsy cases in Moscow was 51 years, and of my 227 necropsy cases in Victoria 62 years. The disease is rare under 30, but Kaufmann mentions patients of 21, 18 and 9 years, and proven cases of 13, 14 and 15 years were reported by Moore, Ness and Tencher, and Laird.

(3) Sex incidence

In nearly all countries the mortality rates from gastric cancer are decidedly higher for men than for women. The Registrar General's figures for England and Wales, 1930-32, show 18,876 male deaths and 9,243 female deaths from this cause, a ratio of 2 to 1. The greater liability of men to the disease is borne out also by surgical and necropsy records. Kaufmann recorded 394 necropsies on males and 227 on females, Poscharissky, 345 and 155 respectively, and my series 157 and 70. The sex ratio of these figures combined is almost exactly 2 to 1. Pack and Le Fevre's clinical series showed a ratio of 2.2 to 1.

(4) Social class and gastric carcinoma

Cancer of the stomach was one of those tumours which according to the Registrar-General's figures, showed a decided class gradient, people in the unskilled classes showing the higher incidence. The standardized mortality ratios in the 5 descending social classes were 59, 84, 98, 108 and 124 for males, and 55, 78, 105, 104 and 120 for married females. That the wives of men in the lower social classes share with their husbands the increased liability to gastric cancer, suggests that the causative factors are connected more with general economic circumstances, home life or diet than with occupation.

SITES OF GASTRIC CARCINOMAS

The situations of the tumours in Stewart's (1931), Poscharissky's and my own series of necropsies were as follow

Site	Stewart	Poscharissky	Willis	Total
Pylorus and antrum -	155	194	125	474 = 47%
Lesser curvature -	40	170	52	262 = 26%
Cardia region -	37	45	21	103 = 10%
Rest of organ -	26	52	11	89 = 9%
Whole stomach -	21	39	18	78 = 8%
	279	500	227	1006

CHAPTER 21

CARCINOMA OF THE STOMACH

CARCINOMA is by far the commonest epithelial tumour of the stomach. Benign epithelial tumours are relatively infrequent and since carcinoma often supervenes in them they will be discussed with the precursors of carcinoma. Konjetzny's admirable monograph (1938) gives a good account of the pathology of gastric carcinoma.

FREQUENCY AGE AND SEX INCIDENCE

(1) Frequency and race incidence

(a) Mortality records

These show that cancer of the stomach is one of the commonest tumours in all European peoples but its frequency as a registered cause of death differs markedly in different countries. The high proportion of errors in the clinical diagnosis of gastric cancer (see Chapter 5) limits the reliability of the mortality figures in comparing the frequency of the disease in different countries but the differences recorded are too great to be accounted for wholly by errors of registration. In Great Britain and in Australia about one quarter of cancer deaths are recorded as due to cancer of the stomach in Scandinavia, Holland, Bavaria, Switzerland and Czechoslovakia more than one half of them the highest proportion being Czechoslovakia's 66 per cent. In USA the proportion is about 10 per cent (Konjetzny and Hoffman, Cramer and the Registrar General, Chapter 5). Gastric cancer is also one of the commonest in Japan, accounting for 75 per cent of recorded cancer in males and 30 per cent in females. It is also very common in the East Indies (Hoffman) but is decidedly less common in the West Indies. The change in *situ* comparable to that in the West Indies.

FIG 177—Epithelium marginalis change in *situ* comparable to that in the West Indies.

Invasion or perforation of the stomach leads to septic pneumonia, pleural cavity, peritonitis, and other complications. Invasive complications of gastric cancer are common. Kaufmann saw 15 males (25 per cent) and 70 out of 425 females (16 per cent) with equal numbers of male and female beds (Table V). In the Japanese and necropsy series from those European countries mortality figures for gastric cancer show correspondingly high figures (up to 70 per cent) for this disease. The frequency of gastric carcinoma cannot be estimated reliably by the number of cases erroneously diagnosed as such. Table I of Chapter 5 shows that in a large general hospital 30 per cent of cases of gastric cancer are misdiagnosed as such.

(1) Metastases in stomach. But it is not justifiable to assume from this that these often occur and negative misdiagnoses will cancel each other out. Special investigations such as radiography, test meal examinations and gastroscopy

(1) Gastric ulceration as a precursor of cancer

The vexed question of the frequency of cancerous change in chronic ulcers and the proportion of cancers which arise in previous ulcers has been fully discussed by Dible, Orator, Stewart, Newcomb and Konjetzny. The following conclusions can I think, be safely made: (a) Routine microscopical study of the margins of chronic gastric ulcers of prolonged history and typical naked-eye appearance reveals evidence of genuine early cancerous change very rarely indeed. (b) Clear examples of localized carcinoma at one part of the margin of an otherwise simple chronic ulcer, and examples of a ring of carcinoma encircling an area of ulceration with a cancer-free fibrous base, are uncommon. (c) The number of cancer specimens encountered which show good evidence of preceding ulceration is small compared with the total number of gastric ulcers encountered. The proportion of presumed ulcer cancers in Stewart's series of 358 operation specimens was 6 per cent; in Orator's series of 330 operation specimens 5 per cent, and in Newcomb's series 4 per cent. But as Stewart said 'It is clear from the frequency with which well-healed scars are encountered in the stomach that the actual proportion of chronic ulcers which become malignant must be much less than this'. (d) The proportion of carcinomas which show acceptable evidence of having been preceded by ulcers is also small—16 per cent in Stewart's operation series and 13 per cent in Newcomb's. (e) The diagnosis of ulcer-cancer should not be made on any single histological criterion, each case must be judged on all the available evidence. Thus Dible in a careful study of 33 early carcinomas, found that the hypothesis of their having arisen in ulcers could be rejected immediately in 19, and could be rejected after thorough microscopical examination in a further 9 cases; in the 5 remaining cases the findings were compatible with a diagnosis of ulcer-cancer but the possibility of an ulcerating sclerosing carcinoma could not be wholly excluded, and in only 2 of these 5 cases was there a long history suggestive of chronic ulceration. Hence, in only 2 of 33 cases (6 per cent) did the whole of the evidence sustain a diagnosis of ulcer-cancer.

Although I have not made careful studies like those cited above, my experience accords with the lowest estimates of the frequency of ulcer-cancer. I have examined many hundreds of gastric ulcers and carcinomas, but have seen only 3 examples of unequivocal ulcer-cancer. During the same period I have seen two instances. Case I and another of the fortuitous coexistence of carcinoma and simple ulcer separate from each other.

Case I—History.—In 1936 a man aged 51 years had haematemesis, and a diagnosis of gastric ulcer was made. A high acid curve was recorded. Haematemesis recurred in 1939, when he was again effectively treated for ulcer. Early in 1941 he developed fever, anaemia and cough with signs suggesting right basal empyema. Test meal showed complete achlorhydria. Blood examination showed—haemoglobin 25 per cent, red corpuscles $1\frac{1}{2}$ million, white corpuscles 85 000 per cubic millimetre, film typical myeloid leukaemia with many immature cells and many nucleated red cells. *Necropsy.*—The stomach contained a fungating carcinoma at and just below the cardia extending into the oesophagus. Separated from the growth by 2 centimetres of healthy mucosa there was a circular opening in the posterior wall of the stomach near the lesser curvature extending deeply into a mass of fused cancerous coeliac lymph glands, the appearance strongly suggesting penetration of the base of a chronic ulcer into the mass of glands. The surrounding tissues contained purulent tracks, one of which extended along the upper border of the pancreas and into the hilum of the spleen, and another opened by a small

In resected stomachs which of course include very few cancers of the cardia or of the upper part of the lesser curvature or of the whole organ, the proportion of pyloric tumours is greater—in Newcomb's series 57.5 per cent and in Stewart's series 76 per cent.

SPONTANEOUS AND EXPERIMENTAL GASTRIC CARCINOMA IN ANIMALS

Surely it is of great significance that while carcinoma of the stomach is one of the commonest tumours in man it is one of the rarest in all other animals. Wells *et al.* reviewed the few reports of the tumour in mice, rats, horses, dogs, bovines, sheep and fowls. Rudduck and I described an adenocarcinoma of the cardia, and Davis and Naylor a diffusely infiltrating pyloric carcinoma, in the dog.

The rarity of spontaneous gastric neoplasms in animals has enhanced the interest of producing these experimentally. The subject, already referred to in Chapter 4, has been dealt with in detail by Peacock and by Nettleship. It must suffice to say here that although it is quite possible that occasional gastric tumours observed in experimental animals after the ingestion of carcinogenic substances may indeed have been caused by these agents, the results are too few to warrant final conclusions, and much more work in this field is required. Such work is of twofold importance: for, if we could discover the conditions necessary for regularly successful production of gastric tumours by known carcinogens, not only might these conditions be found applicable in human pathology, but they might also lead to dependable methods for the biological testing of foods and other ingesta for the presence of as yet unidentified carcinogens. Peacock's and Nettleship's papers show the complexity of the possible causative factors which it may be necessary to reduplicate in order to obtain experimental tumours comparable with human gastric carcinoma. These will now be discussed.

POSSIBLE CAUSATIVE FACTORS IN GASTRIC CARCINOMA

The diets and dietetic habits of civilized man are unnatural in many respects. The substances introduced into the human stomach are endless in their variety, quantity and physical state. The problem confronting the research worker in elucidating the causation of gastric diseases is therefore enormous and complex. He must consider not only the more usual food substances and their possible products under different physical conditions (cooked, smoked, tinned, frozen, etc.) but also a vast number of drugs, antiseptics, dyes, flavouring agents, bacteria and bacterial products which we consume in large amounts. It is not surprising then that many and diverse hypotheses abound, but little real knowledge has been gained of the causation of secretory disturbances, inflammation, ulceration and carcinoma of the stomach, and of the interrelationships of these several kinds of lesions. In the following discussion we will deal first with the pre-cancerous proclivities of the more obvious structural lesions of the stomach—ulcer, gastritis and benign tumours—and then with the less tangible dietetic and other factors, the consideration of many of which is applicable to the oesophagus also.

microscopical study discloses carcinomatous changes in about one quarter of them (as in the specimen of Fig 178), but also from their association with frank carcinoma. Thus, in Stewart's series of 56 stomachs with polypi, cancer was also present in 15 cases (27 per cent), while in 322 cancerous stomachs polypi were



FIG 178—Glandular polypus removed surgically from the stomach of a man of 50 years. A shows glands with chief and oxyntic cells. B shows large goblet-celled glands ($\times 120$)

present in 15 (5 per cent). Spriggs distinguished between multiple polypi and polypoid or hypertrophic gastritis, the latter is inflammatory, often subsides, and is not specially prone to cancerous change. The following case is of interest in that gastric and colonic polypi and cancer of the colon coexisted.

Case II—Male, aged 78. *Necropsy*—Stomach contained 5 separate polypoid growths, the largest 1 centimetre in diameter. Small intestine normal. Ascending colon contained 8 separate pedunculated polypi, the largest 2 centimetres in diameter, and a flat area of papillary growth 3 centimetres in diameter without metastases. *Microscopy*—Gastric polypi were columnar-celled and goblet-celled papillomas with however several areas suspicious of early malignancy. Intestinal polypi were benign, but the flat growth was an adenocarcinoma still restricted to the mucosa and submucosa.

(b) *Adenomyoma " of the stomach*

This is a rare lesion described by Stewart and Taylor. It appears as a localized but ill defined thickening in the pyloric region which simulates scirrhus carcinoma. The thickening is confined, however, to the muscle coat and the overlying mucosa is normal. Microscopically it shows well differentiated glandular structures of mingled ductular, Brunner and pancreatic type with abundant intervening smooth muscle. The lesion is a heterotopia rather than a neoplasm and appears to be no more liable to cancerous change than are the heterotopic masses of pancreatic

discharging sinus into the first part of the duodenum. No metastases other than the lymph nodal deposits were found. *Microscopy*—Spheroidal-celled carcinoma and adenocarcinoma, no growth in the margins of the ulcer. *Comment*—Points of interest were the development of achlorhydria during the course of the disease, the fortuitous coexistence of ulcer and cancer, and the simulation of a leukaemic blood picture by an extravagant leucocytosis in an anaemic patient.

Such fortuitous coexistence of contiguous ulcer and cancer still further reduces the significance of ulcer as a pre cancerous lesion. Again Mallory pointed out that peptic ulceration in an area of pre invasive carcinoma might lead to appearances in every way simulating those of 'ulcer cancer'. In my opinion then, Stewart's estimate that 16 per cent of cancers arise in ulcers is likely to be an over estimate, and Dible's estimate of 6 per cent is likely to be nearer the truth. Chronic ulcer must be regarded as only an occasional precursor of cancer, perhaps it does no more than determine the localization of neoplasia in a stomach already prepared for it in a way analogous to the Deelman phenomenon in the skin (see Chapter 4).

(2) Gastritis as a precursor of cancer

Konjetzny, Orator and Hurst have been the chief proponents of the view that chronic gastritis is a frequent pre cancerous lesion. This view has been opposed by Wanser, Hebbel and Guiss and Stewart on the grounds that microscopical evidence of gastritis is very frequent in middle aged and elderly people, that the gastritis often seen in cancerous stomachs is non-distinctive and variable in degree and extent, that inflammatory changes in cancerous organs must often be secondary to the tumours, and that some early carcinomas are unaccompanied by gastritis. However, some of Konjetzny's beautiful photographs depicting atrophic hyperplastic gastritis with pronounced polypoid changes passing into carcinoma certainly support his view, and his full and critical discussion of the question cannot be lightly dismissed. He regards ulcer-cancer as only a special example of gastritis cancer, the three lesions—gastritis, ulcer and cancer—having a close but variable causal relationship to one another. Further thorough studies of stomachs with early carcinomas are needed in order to assess the significance of gastritis as a precursor of neoplasia.

(3) Benign epithelial neoplasms and carcinoma of the stomach

(a) Papillomas and adenomas

These are only variants of the same group of benign epithelial tumours of the gastric mucosa. They show combinations of solid glandular and papillary structure, which includes columnar celled epithelium resembling that of the inner surfaces of the stomach and masses of gastric or pyloric glands (Fig. 178). Their structure, distribution and proneness to malignant change have been fully described by Stewart, Miller *et al.* and Spriggs. They are situated usually in the body or pre pyloric part of the stomach, they are single in about one half and multiple in about one half of the cases, they are more common in men than in women, and the mean age of patients is about 55. Their great tendency to become cancerous is apparent not only from the fact that

Commenting on their findings, Wilkinson (1945) maintained his earlier opinion that the development of gastric cancer, like that of other serious diseases in patients under treatment for pernicious anaemia is largely fortuitous. In 1,600 consecutive patients under regular observation he saw cancer develop in only 28, of these, 12 (0.75 per cent) had cancer of the stomach after periods of from 1 to 17 years, with an average period of 7.7 years, and 9 of the 12 were over 60 years of age when the cancer was diagnosed. Cancer occurred in the large intestine in 5 cases, all of whom were elderly. Diabetes developed in 28 cases, and thyroid disease in 36.

In my opinion, the evidence that true pernicious anaemia or achlorhydria predisposes to carcinoma of the stomach is inconclusive. The prolongation of the life of pernicious anaemia patients by modern therapy means inevitably that they will die of other old age diseases, of which cancer of the stomach is one of the commonest. It must be remembered too that gastric carcinoma, with or without metastases in bone marrow, may produce a macrocytic hyperchromic anaemia which has often been mistaken for pernicious anaemia (see p. 409), and that, although this tumour is often fatal within two years, some patients survive for much longer periods as in the following case.

Case III—History—In October 1921 a man aged 65 began to suffer from indigestion, vomiting and loss of weight. Laparotomy in December showed inoperable gastric carcinoma and the patient was admitted as incurable to the Austin Hospital, Melbourne, where however he survived until 1929, his progress being briefly as follows. X-ray examinations on several occasions showed an enlarging filling defect of the pyloric half of the stomach with evidence of pyloric obstruction. Fractional test meals on several occasions showed free hydrochloric acid present usually attaining its peak at 2 hours. Progressive hypochromic anaemia appeared with haemoglobin down to 30 per cent and red corpuscles to 2 million per cubic millimetre. Nevertheless he gained weight, and with the passage of time doubt of the diagnosis of cancer was entertained. Early in 1928 retention of urine appeared evidently due to prostatic enlargement; this became steadily worse and the urine increasingly purulent in spite of bladder wash-outs. The patient died in March 1939 at the age of 73 and 7½ years after onset of symptoms of gastric disease. *Necropsy*—Bulky gelatinous adenocarcinoma of pyloric half of stomach with nodular infiltration of the lesser omentum but no metastases. Cause of death—prostatic enlargement, suppurative pyelonephritis.

Cases of gastric cancer of long duration, like the foregoing, show that an interval of several years between the appearance of anaemia and the discovery of a gastric neoplasm cannot be taken as conclusive proof that the former preceded the latter. The only cases in which it can be claimed with certainty that the anaemia preceded the tumour are those in which typical blood changes, including leucopenia, and a typical response to liver therapy were observed several years prior to the appearance of the tumour, and in which expert radiographic examination of the stomach initially showed no abnormality. Some of the cases reported fulfil these criteria, but are they so numerous that they cannot be accounted for by the fortuitous development of a tumour which is very common in elderly people? This is still arguable and further carefully evaluated data are necessary before final decision can be reached.

(5) Possible carcinogenic substances ingested

The needle in the haystack simile is particularly appropriate to the search

tissue found in the stomach intestine or Meckel's diverticulum Nicholson described and referred to cases of carcinoma of heterotopic pancreatic tissue

(4) Pernicious anaemia and achlorhydria as precursors of cancer

In 1929 Hurst advanced the view that the achlorhydria frequently accompanying gastric carcinoma was not the result of the tumour but had preceded it. He cited cases in which achlorhydria had been known to be present in patients who later developed gastric cancer, and others in whom pernicious anaemia preceded cancer, and he supposed the achlorhydria to result from previous chronic gastritis. He also described cases of ulcer cancer in which the acidity was undiminished by the onset of the cancer and concluded that 'when free acid is present the carcinoma is likely to be secondary to ulcer and when achlorhydria is present it is generally secondary to gastritis'. However, that the achlorhydria which often accompanies gastric carcinoma does not always precede the tumour is shown by Case I above, and by that cited by Stewart in which hyperchlorhydria was known to have been present 24 years prior to laparotomy, by which time achlorhydria had developed and necropsy showed an ulcer cancer. I know also of other cases in which achlorhydria developed during the course of carcinoma of the stomach.

Relevant here are observations on the gastric secretions of groups of people differing in their liability to gastric cancer. Lintott found no significant difference between the test meal analyses of English and Dutch people or between those of the upper and poorer classes. Although the Chinese and Malays in Java differ markedly in the incidence of both ulcer and cancer of the stomach, Bonne *et al* found no differences between the two races as regards either gastric secretion or the structure of the gastric mucosa.

In 1933 Wilkinson gave a detailed account of the diseases he had observed to develop in 370 cases of pernicious anaemia. These included 8 cases of carcinoma the sites of which were the buccal cavity in 3 cases, stomach in 2, uterus in 2 and colon in 1 case. He regarded the association of pernicious anaemia and malignant disease as largely fortuitous.

In 1938 Washburn and Rozendaal reported that in 906 consecutive cases of pernicious anaemia gross gastric lesions had been found in 24 comprising carcinoma in 16 and polypi in 8, and from the literature they collected references to 75 cases of coexisting pernicious anaemia and gastric carcinoma. They gave details of 7 of their patients in whom the anaemia had long antedated the development of carcinoma. Spriggs also commented on the frequently reported association of gastric polypi with pernicious anaemia.

In 1945 Kaplan and Rigler reviewed the subject afresh and reported 293 necropsies on cases of pernicious anaemia of which 36 had carcinoma of the stomach a proportion thrice the expected. Kaplan and Rigler therefore concluded that there is a definite causative relationship between pernicious anaemia and gastric cancer and recommended that patients with pernicious anaemia should be submitted to regular clinical and X-ray examination to detect early new growths of the stomach. Rigler *et al* by carrying out this suggestion on 211 patients claimed to detect carcinoma in 8 per cent and polypi in 7 per cent. The diagnosis of pernicious anaemia in Kaplan and Rigler's series however, is questionable for some of their cases perhaps some cases of carcinoma with a pernicious like anaemia were included.

Commenting on their findings, Wilkinson (1945) maintained his earlier opinion that the development of gastric cancer, like that of other serious diseases in patients under treatment for pernicious anaemia is largely fortuitous. In 1,600 consecutive patients under regular observation, he saw cancer develop in only 28 of these, 12 (0.75 per cent) had cancer of the stomach after periods of from 1 to 17 years with an average period of 7.7 years, and 9 of the 12 were over 60 years of age when the cancer was diagnosed. Cancer occurred in the large intestine in 5 cases, all of whom were elderly. Diabetes developed in 28 cases, and thyroid disease in 36.

In my opinion the evidence that true pernicious anaemia or achlorhydria predisposes to carcinoma of the stomach is inconclusive. The prolongation of the life of pernicious anaemia patients by modern therapy means inevitably that they will die of other old age diseases of which cancer of the stomach is one of the commonest. It must be remembered too that gastric carcinoma, with or without metastases in bone marrow, may produce a macrocytic hyperchromic anaemia which has often been mistaken for pernicious anaemia (see p. 409), and that, although this tumour is often fatal within two years, some patients survive for much longer periods, as in the following case.

Case III—History.—In October 1921 a man aged 65 began to suffer from indigestion, vomiting and loss of weight. Laparotomy in December showed inoperable gastric carcinoma and the patient was admitted as incurable to the Austin Hospital, Melbourne, where however he survived until 1929, his progress being briefly as follows. X-ray examinations on several occasions showed an enlarging filling-defect of the pyloric half of the stomach with evidence of pyloric obstruction. Fractional test meals on several occasions showed free hydrochloric acid present, usually attaining its peak at 2 hours. Progressive hypochromic anaemia appeared with haemoglobin down to 30 per cent and red corpuscles to 2 million per cubic millimetre. Nevertheless he gained weight, and with the passage of time doubt of the diagnosis of cancer was entertained. Early in 1928 retention of urine appeared, evidently due to prostatic enlargement; this became steadily worse and the urine increasingly purulent in spite of bladder wash-outs. The patient died in March 1939 at the age of 73 and 7½ years after onset of symptoms of gastric disease. *Necropsy.*—Bulky gelatinous adenocarcinoma of pyloric half of stomach with nodular infiltration of the lesser omentum but no metastases. Cause of death—prostatic enlargement, suppurative pyelonephritis.

Cases of gastric cancer of long duration like the foregoing show that an interval of several years between the appearance of anaemia and the discovery of a gastric neoplasm cannot be taken as conclusive proof that the former preceded the latter. The only cases in which it can be claimed with certainty that the anaemia preceded the tumour are those in which typical blood changes, including leucopenia and a typical response to liver therapy, were observed several years prior to the appearance of the tumour, and in which expert radiographic examination of the stomach initially showed no abnormality. Some of the cases reported fulfil these criteria, but are they so numerous that they cannot be accounted for by the fortuitous development of a tumour which is very common in elderly people? This is still arguable, and further carefully evaluated data are necessary before final decision can be reached.

(5) Possible carcinogenic substances ingested

The needle in the haystack simile is particularly appropriate to the search

for possible carcinogens in human ingesta. There are two principal methods of attacking the problem—(a) clinical inquiries like those of Craver, Herbert and Bruske, into the diets (including alcohol drugs etc.) of patients with gastric or oesophageal cancer or of communities particularly prone to these tumours with adequate control series for comparison and (b) experimental inquiry aiming at the production of gastric tumours by factors comparable with those operating in man as discussed by Peacock, Nettleship and Kirby. Although a beginning has been made along both of these lines of inquiry little of positive value has yet emerged. A great field awaits exploration and so diverse and complex are the problems that significant results will be attained only by extensive, carefully designed and well informed research. Some of the possible factors involved deserve brief mention.

(a) *Alcohol*

Alcohol has often been suggested as a possible cause of oesophageal and gastric as well as of buccal and pharyngeal tumours. Some evidence for this suggestion is afforded by (a) the high mortality rates from oesophageal and gastric cancer recorded for dock labourers furnacemen stevedores barmen and some other occupational groups supposed to be specially addicted to alcoholic drinks and the low mortality rates from these tumours recorded for dentists doctors civil servants teachers professional engineers draughtsmen barristers typists and clerks (Registrar General's Decennial Supplement 1938) (b) the alcoholic habits recorded of patients with oesophageal cancer by Craver and others and (c) the heavy consumption of alcohol, especially as strong spirits, by the Dutch and some other peoples with a high incidence of gastric cancer. All of this evidence however is no more than strongly suggestive. Many factors other than alcohol may be concerned in the differences in question. Supposing that alcoholic drinks are indeed a real factor in the causation of oesophageal and gastric cancer it may yet be that the alcohol itself is less to blame than other ingredients of various spirits wines and liqueurs or that the concentration of the alcohol is an important factor. Perhaps Daniel Quilp who drank Schiedam strong and fiery as raw spirit and could swallow half a pint of boiling rum neat avoided cancer of his stomach only by drowning!

(b) *Carcinogenic hydrocarbons*

These must be considered as possible ingredients of foods. Kennaway's finding that many kinds of organic substances heated to charring temperatures yielded carcinogenic artificial tars is surely not without culinary significance. Roasting grilling frying and toasting may well produce in small quantities the same carcinogens as were present in Kennaway's artificial tars and the life long ingestion of these may be a major cause of our common alimentary cancers. Fats used repeatedly for frying would seem to be the most likely material in which to commence the search for possible carcinogens and Peacock Kirby and Beck (cited in Chapter 4) have already published promising preliminary work of this kind. Smoked fish also should certainly be investigated. Other possible sources of ingested carcinogenic hydrocarbons include tobacco tar, dust from tarred roads and domestic and occupational soots and smokes.

(c) *Other chemical carcinogens*

These may exist amongst the great variety of drugs, flavouring agents colouring agents and preservatives which man consumes. Biological testing of all suspect substances will be necessary to detect the offenders.

The supposition that ingested non absorbable, or only slightly absorbable, chemical carcinogens may be largely to blame for alimentary malignancies has much to commend it on theoretical grounds. Admitted to the stomach such substances would often remain in contact with its mucous membrane for several hours at a time. In the small intestine, however, they would be considerably diluted and hurried through the bowel quickly. In the large intestine they would again be concentrated and would lie in contact with the mucosa for long periods. This would accord with the relative frequency of cancer of the stomach, large intestine and small intestine. It would also accord with the rarity of all alimentary cancers in animals, whose food is seldom fried, roasted or smoked, and who do not consume large amounts of drugs, dyes, flavouring and preserving agents or tobacco.

(6) *The physical state of ingested food*(a) *Temperature*

The temperatures at which fluids can be imbibed with comfort are surprisingly high. Personal experiments show that fluids at 50° C (i.e. the temperature of a 'scalding hot' bath) are 'luke warm' to drink, at 65° C (pasteurizing temperature) 'comfortably hot' to drink, and that at 75° C (blistering temperature for the skin) fluids feel 'very hot' but can be swallowed without apparent injury. A piece of unmasticated food such as a lump of potato or meat, can be swallowed while its internal temperature is only a few degrees below boiling point. Clearly then the oesophagus and stomach are constantly being subjected unwittingly to thermal insults of a degree which our skins would not tolerate. Whether such insults may be directly or indirectly carcinogenic remains to be proved. Craver's inquiries suggested that food temperatures may have played some part in the causation of gastric cancers but not in that of oesophageal cancers. Herbert and Bruske found that the Dutch take their food hotter than the English.

(b) *Imperfect mastication*

Imperfect mastication, resulting either from habitual haste or from dental disease or lack of teeth, no doubt occasions repeated minor injuries of the oesophagus or stomach. It is indeed surprising what people will swallow whole. I have found impacted against a stenosing carcinoma of the colon a collection of cherry stones along with the intact bones of most of the limbs and trunk of a rabbit! Craver found poor teeth or lack of teeth to be the most prominent item revealed by his inquiry in cases of gastric cancer, and one of the most prominent in oesophageal cancer. Yet as far as I know, there is no evidence that hair eaters or lunatics who swallow foreign bodies are predisposed to cancer of the oesophagus or stomach. Moreover cattle, goats, sheep and other herbivores often ingest and retain many kinds of foreign bodies yet gastric tumours are as infrequent in them as in other animals.

for possible carcinogens in human ingesta. There are two principal methods of attacking the problem—(a) clinical inquiries like those of Craver, Herbert and Bruske into the diets (including alcohol drugs etc.) of patients with gastric or oesophageal cancer or of communities particularly prone to these tumours with adequate control series for comparison and (b) experimental inquiry aiming at the production of gastric tumours by factors comparable with those operating in man as discussed by Peacock, Nettleship and Kirby. Although a beginning has been made along both of these lines of inquiry, little of positive value has yet emerged. A great field awaits exploration and so diverse and complex are the problems that significant results will be attained only by extensive carefully designed and well informed research. Some of the possible factors involved deserve brief mention.

(a) *Alcohol*

Alcohol has often been suggested as a possible cause of oesophageal and gastric as well as of buccal and pharyngeal tumours. Some evidence for this suggestion is afforded by (a) the high mortality rates from oesophageal and gastric cancer recorded for dock labourers furnacemen stevedores barmen and some other occupational groups supposed to be specially addicted to alcoholic drinks, and the low mortality rates from these tumours recorded for dentists, doctors, civil servants teachers professional engineers draughtsmen barristers typists and clerks (Registrar General's Decennial Supplement 1938) (b) the alcoholic habits recorded of patients with oesophageal cancer by Craver and others and (c) the heavy consumption of alcohol especially as strong spirits by the Dutch and some other peoples with a high incidence of gastric cancer. All of this evidence however is no more than strongly suggestive many factors other than alcohol may be concerned in the differences in question. Supposing that alcoholic drink are indeed a real factor in the causation of oesophageal and gastric cancer it may yet be that the alcohol itself is less to blame than other ingredients of various spirits wines and liqueurs or that the concentration of the alcohol is an important factor. Perhaps Daniel Quilp who drank Schiedam strong and fiery as raw spirit and could swallow half a pint of boiling rum neat avoided cancer of his stomach only by drowning.¹

(b) *Carcinogenic Hydrocarbons*

These must be considered as possible ingredients of foods. Kennaway's finding that many kinds of organic substances heated to charring temperatures yielded carcinogenic artificial tars is surely not without culinary significance. Roasting grilling frying and toasting may well produce in small quantities the same carcinogens as were present in Kennaway's artificial tars, and the life long ingestion of these may be a major cause of our common alimentary cancers. Fats used repeatedly for frying would seem to be the most likely material in which to commence the search for possible carcinogens and Peacock Kirby and Beck (cited in Chapter 4) have already published promising preliminary work of this kind. Smoked fish also should certainly be investigated. Other possible sources of ingested carcinogenic hydrocarbons include tobacco tar, dust from tarred roads and domestic and occupational soots and smokes.

Bowen's disease of the epidermis and clearly shows simultaneous or successive cancerous change over a wide field of mucous membrane. The very diffuse forms of gastric carcinoma such as "gizzard" or "leather bottle" stomach owe their wide extent not solely to their infiltrative growth but also to their widespread



FIG. 179—Three parts of highly differentiated adenocarcinoma infiltrating gastric muscle, from a diffusely infiltrating growth in a man of 52 years ($\times 120$)

origin. Discussion as to whether carcinomas arise mainly from glands or from the surface epithelium is pointless, it is clear from the study of early non-invasive growths that the whole of the epithelium in the affected area participates.

THE STRUCTURE OF GASTRIC CARCINOMA

(1) Macroscopic forms of growth

For descriptive purposes the following forms may be distinguished

- (1) Polypoid or fungoid carcinomas of predominantly endogastric growth
- (2) Ulcerated plateau like carcinomas, with prominently elevated rampart like nodular borders

(7) Heredity and gastric cancer

Inherited predisposition to gastric carcinoma, revealed by occasional cancer families or by the slightly enhanced expectation of this disease appearing amongst the immediate relatives of sufferers from it (see Chapter 5) is certainly not a very important factor in causation. Of historical interest is the predisposition of the Bonaparte family to gastric carcinoma. Although doubt of the diagnosis of cancer in Napoleon's case has been expressed in my opinion Antommarchi's full description of the post mortem findings (cited by Chaplin) makes it clear that the disease was indeed an extensive carcinoma of the lesser curvature and adjacent walls spreading to the surrounding peritoneum and lymph glands. The little epiploon was contracted swollen, extremely hard and degenerated. The lymphatic glands of this peritoneal covering those which are placed along the curves of the stomach and those which are around the pillars of the diaphragm were in part tumefied and scirrhus and some even in a state of suppuration. Sokoloff collected the medical histories of Napoleon's relatives. His father died at the age of 39 with cancer of the stomach proved by necropsy. His youngest sister Caroline also died of gastric cancer. Two other sisters Elisa and Pauline died at ages of 43 and 44 years of gastric disease from their histories almost certainly carcinoma and one of his brothers Lucien died at 65 probably of carcinoma of the stomach.

THE MODE OF ORIGIN OF GASTRIC CARCINOMA

Hauser, Verse, Konjetzny and others have all described specimens which show plainly that gastric carcinoma may arise in a widespread or multicentric manner from more or less extensive areas of mucous membrane. According to Konjetzny multicentric development of gastric carcinoma is the rule, an opinion which is convincingly supported by his many excellent illustrations. He gives references also to recorded cases of grossly multiple carcinomas to which may be added Tsunoda's case of three separate areas of cancer in a stomach, and the following two cases.

Case IV—Male aged 64. *Necropsy*—Stomach showed (i) irregular ill-defined area of flat growth 7 centimetres in diameter on anterior wall near cardia involving all coats and producing plaque like thickening of serous coat. (ii) a similar ill-defined region of thickening on the greater curvature near the pylorus. (iii) intervening gastric wall healthy. Perigastric and lumbar lymph gland were enlarged by growth but there were no other metastases. *Microscopy*—Diffusely infiltrating spheroidal-cell carcinoma in both areas of stomach with more cellular deposits in lymph glands.

Case I—Female aged 64. *Necropsy*—Stomach showed (i) a projecting fungoid growth 5 centimetres in diameter attached by an infiltrated pedicle 3 centimetres in diameter to the greater curvature 3 centimetres proximal to the pylorus and with several enlarged cancerous lymph glands in the adjacent omental attachment. (ii) an irregular growth involving most of the circumference of the cardia with no accompanying lymph nodal deposits. (iii) intervening stomach wall healthy. Liver contained a few scattered metastases. All other organs clear. *Microscopy*—Both gastric tumours and the hepatic metastases showed disorderly adenocarcinoma.

Schneider described two separate histologically different carcinomas in one stomach and referred to 9 similar reports. Cancerous change in a polypus is often demonstrably widespread or progressive. Non polypoid pre-invasive carcinoma or carcinoma *in situ* as described by Mallory is analogous to

variants are seen

- (a) *Adenocarcinoma* or *adeno papillary carcinoma* showing distinct differentiation of acinar structures of varying degrees of perfection (Figs 32 and 179)
- (b) *Mucoid adenocarcinoma*, a variant of (a) in which mucus secretion is prominent, often producing large amounts of extra cellular gelatinous mucus in parts of which only scanty isolated groups of tumour cells are present

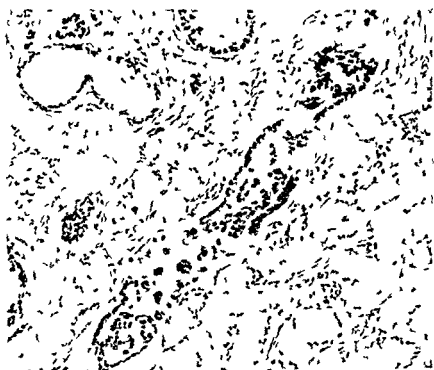


FIG 181 —Pyloric carcinoma invading duodenum amidst Brunner's glands ($\times 120$)

- (c) *Signet ring cell carcinoma*, consisting mainly of spherical mucus containing cells with their nuclei thrust to one side (Figs 44 50, 180, 182 and 183)
- (d) *Infiltrating spheroidal-cell carcinoma*, identical with (c) except that the cells show little or no secretion, secreting and non secreting spheroidal cells are often seen together especially in the diffuse forms of growth
- (e) *Metaplastic squamous cell carcinoma* is rare in the stomach, usually in parts only of a tumour of mainly adenocarcinomatous structure
- (f) *Highly cellular anaplastic carcinoma* is frequent, forming soft, necrotic or haemorrhagic growths consisting of disorderly masses of rapidly multiplying poorly differentiated cells with little or no glandular orientation. Some haemorrhagic tumours of this kind have had a misleading chorion-epithelioma like appearance, especially in their metastases in the liver (Risèl Stewart 1913, Gaertner)

It must be emphasized that the names (a) to (f) do not denote entities but only structural variants of the entity *gastric carcinoma*, and that several or all of them may be seen in a single tumour. I agree with Stout that 'it is not only a

- (3) Ulcer like carcinomas without prominent ramparts or well defined borders but with diffuse infiltration of the neighbouring stomach walls
- (4) Extensive diffuse carcinomas producing more or less uniform thickening of part or whole of the stomach walls with only slight superficial ulceration or none at all

These gross forms are of course, not sharply distinct tumours showing various combinations of them are common. Microscopically group (1) shows mainly adeno papillary structure group (4) mainly infiltrating spheroidal celled or signet ring celled structure while groups (2) and (3) show all possible structural



FIG 180—Signet ring-cell mucoid carcinoma of stomach ($\times 72$)

variants. Mucus secretion may be visible to the naked eye in any of the forms of growth, but is most conspicuous in group (2) producing massive irregular gelatinous tumours. The commonest situation of diffuse carcinomas, when these are restricted to part only of the wall of the stomach is the pyloric part whence they spread more or less extensively towards the cardia. When they affect most or the whole of the organ they produce the gizzard or leather bottle stomach often with great contraction and rigidity of the organ. In spite of the great thickening of the wall often up to 2 centimetres or more the various coats especially the muscular layers often remain clearly distinguishable on the cut surface. Indeed, in many cases the prominently thickened muscle layers appear to have undergone hypertrophy.

(2) Microscopic structure

All carcinomas of the stomach are of course glandular in origin but the extent to which glandular differentiation appears in them varies widely from tumour to tumour and also in different parts of one tumour. The following structural

tubules a carcinoma shall form before it is to be called adenocarcinoma? How much mucin must be secreted in order that a tumor shall be called a colloid or mucoid carcinoma?" I also agree with him that attempts to predict the degree of malignancy, the rate of growth and the probable success or failure of surgical treatment based on cellular differentiation alone are of very little value when applied to an individual case, although some small percentage of difference may appear in large groups

THE DIRECT SPREAD OF GASTRIC CARCINOMA

Besides diffuse spread in the walls of the stomach itself, gastric cancers extend also into the walls of the duodenum and oesophagus and into the gastrohepatic and gastrocolic omenta, the pancreas, spleen, transverse colon, liver and diaphragm

The prevalent view that carcinoma of the stomach seldom extends into the duodenum is false. Microscopical examination of resected stomachs as well as those obtained at necropsy will often disclose infiltration of the duodenal submucous or muscle coats for distances of 2 centimetres or more beyond the pylorus (examples and references by Castleman, and Figs 34 and 181). This is of practical importance, it means that all gastrectomies for pyloric carcinomas should include if possible a duodenal cuff of 3 centimetres, and that this should be examined microscopically for extensions of the growth.

Some carcinomas of the cardia region spread grossly into the lower part of the oesophagus, and may simulate primary oesophageal growths. In other cases, extensions of growth take place through the lymphatics or veins of the submucous and muscle coats and lead to areas of ulceration in the oesophagus which appear to be separate from the main growth in the stomach.

Direct extension of gastric carcinomas to the investing peritoneum and to the greater and lesser omenta is of course very common and is the usual source of trans peritoneal dissemination. Many pyloric growths also invade the pancreas directly and invasion of the bile duct or of the portal vein or its main tributaries is not unusual. Through the gastrocolic omentum the transverse colon may be invaded and gastrocolic fistula may develop. Direct invasion of contiguous parts of the liver occurs frequently. Perforation of gastric cancers into the peritoneal cavity, an accident much less common than with chronic ulcers has been well described by Aird.

Invasion of the spleen may take place either directly from the primary growth or from deposits in the splenic lymph glands. The growth usually enters the spleen at its hilum and spreads mainly along its trabeculae, and the trabecular extensions may reach even to the capsule of the convex surface of the organ. The main trabecular veins often suffer invasion. I have seen four cases in which sloughing splenic tissue formed part of the floor of ulcerating cancers of the stomach and serious—in two cases fatal—haemorrhage had taken place from the necrotic spleen.

Lymphatic permeation is often plainly visible in the neighbourhood of gastric carcinomas, appearing as finely nodular white lines on the peritoneal surface of the stomach itself or in the omenta adjacent to it. Microscopical study reveals that from some of the diffusely infiltrating growths very widespread permeation

waste of time but also deceptive to attach histologically descriptive adjectives and prefixes to gastric carcinomas. Who is to determine what proportion of



FIG. 182.—From a Krukenberg tumour of the ovary in a woman of 59 years showing signet ring-cells within lymphatics. Ovarian stroma and part of a corpus albicans also are visible ($\times 120$)



FIG. 183.—From lung of same case as Fig. 182 showing perivascular lymphatics distended by signet ring-cells and mucus. ($\times 120$)

(3) Transperitoneal metastasis

Peritoneal dissemination from gastric carcinoma is very frequent, it had occurred in 26 of my 85 necropsy cases (31 per cent), and in 61 of Stout's 143 cases (43 per cent). It produces scattered discrete nodules, extensive plaque like infiltrations or massive gelatinous collections with or without ascites. Hernial sacs sometimes share in the peritoneal dissemination, and deposits in the rectovesical or recto uterine pouch may simulate primary carcinoma of the rectum (Konjetzny pp 181 2, and references in Chapter 10). Secondary growths in or near the umbilicus may be due to spread from peritoneal deposits on the round ligament of the liver.

Ovarian metastases

These occur more frequently from gastric carcinoma than from any other tumour and in most cases they arise by the trans peritoneal route. For full accounts and many examples see Glockner, Stone Gauthier Villars Willis (1934, Chapter XXIII), and Konjetzny (1938, pp 184 6). Gastric cancer was responsible for 75 of the 133 cases of secondary growths in the ovaries reviewed by Stone, for 247 of the 365 cases of alimentary cancer with ovarian metastases reviewed by Gauthier Villars, and for 6 of my 16 necropsy cases with secondary carcinoma in the ovaries (1941). Thus, at least one third, possibly one half, of all secondary growths in the ovaries are from carcinoma of the stomach. The proportion of cases of gastric carcinoma with ovarian metastases has varied in different series from 3 per cent (Poscharissky) to 14 per cent (Stout), but these series included cases of both sexes and the incidence of ovarian metastases in females only is more than double these figures, e.g. in Poscharissky's series 16 of 155 cases (10 per cent). My 6 cases with ovarian metastases occurred in a consecutive series of 28 necropsies on women with gastric cancer, a frequency of 21 per cent. The mean age of patients with secondary growths in the ovaries is decidedly less than the mean age of the subjects of gastric cancer in general, the former being between 35 and 40 and the latter in the sixth decade (Willis, p 306. Konjetzny p 184) clearly the functionally active ovary is more prone to metastasis than is the senile ovary.

The gross and microscopical structures of the ovarian metastases of gastric carcinoma vary greatly. Some are acinar adenocarcinomas with or without cystic or papillary characters. Many others however show in whole or part the distinctive structure of the *Krukenberg tumour*. In 1896 Krukenberg described as "fibrosarcoma mucocellulare carcinomatodes" a diffusely infiltrating often bilateral solid tumour of the ovaries of myxomatous appearance, consisting of mucus containing signet ring cells scattered amidst abundant oedematous ovarian stroma. Krukenberg believed these tumours to be ovarian in origin but later study showed that most probably all of them are metastatic growths and that carcinoma of the stomach is by far their commonest source (Major Shaw and other references by Willis 1934, pp 310 312). The term Krukenberg tumour should be reserved for growths showing the characteristic structure (Fig 182) and should not be applied—as has often been done—to other kinds of secondary carcinoma in the ovaries. On the other hand Krukenberg tumours are not sharply distinct from other metastatic growths for tumours of combined

of lymphatics has taken place in all the surrounding tissues, and occasionally almost body wide lymph vessel carcinosis is present (Schuerge Schmucker Dawson). In such cases however, permeation has not proceeded solely from the primary growth but also from many metastatic foci established by embolism in lymph glands or lymphatic plexuses (see Chapter 9)

THE METASTASIS OF GASTRIC CARCINOMA

(1) Metastasis to the regional lymph glands

Even in operation specimens the perigastric lymph glands are found to contain tumour in the majority of cases, the proportions lying between 50 and 70 per cent in most series. In necropsy cases the percentage is of course higher, e.g. in 76 of 85 cases which I reported in 1941 (89 per cent) in an identical proportion of Stout's 143 cases, and in 68 per cent of Poscharissky's 500 cases. The presence or absence of lymph nodal metastases can be determined only by careful dissection and microscopical examination and most estimates of the frequency of metastases are under estimates (Fig. 44). Lymphatic metastasis is the main factor affecting the prognosis of resectable tumours. e.g. Walters *et al* found that of 919 operation cases without deposits in the glands 43 per cent survived 5 years or longer but of 1049 cases with affected glands only 16 per cent survived for 5 years. Most of the few 5 year survivors may be regarded as permanently cured but Pain reported a case of recurrence 12 years after partial gastrectomy—whether from residual growth or from fresh cancerous change in the remainder of the organ is uncertain.

(2) Further metastasis by lymphatic channels

From the perigastric lymph glands the tumours often spread quickly and widely to the coeliac lumbar, mesenteric pelvic and mediastinal glands. From the coeliac upper lumbar and mesenteric glands invasion of the cisterna chyli or its main tributaries often occurs and gastric carcinoma is responsible for about one third of the cases of cancerous disease of the thoracic duct (Willis 1934, Chapter III). About 10 per cent of necropsy cases of cancer of the stomach show invasion of the cisterna chyli e.g. 7 of 85 cases (Willis, 1941). Affection of the thoracic duct or its main tributaries often results in embolic dissemination to the lungs and thus partly accounts for the fact that gastric cancer is the tumour most often responsible for miliary carcinosis of the lungs.

Troisier's sign, enlargement of the supraclavicular lymph glands usually of the left side in cases of abdominal malignant disease (Troisier 1889) is most often due to carcinoma of the stomach and in most cases is associated with involvement of the thoracic duct. Its frequency is estimated variously as between 3 and 15 per cent of fatal cases e.g. in 5.4 per cent of Poscharissky's series and in 13 of my 85 cases (15 per cent).

Gastric carcinoma is one of the most frequent sources of secondary growths in the abdominal walls especially in or near the umbilicus. In most cases these are due to lymphatic dissemination along the round ligament but in some cases they arise by direct spread from the primary growth or from peritoneal metastases (See Quénu and Longuet 1896 Willis 1934, pp. 386-7, and Konjetzny, 1938, p. 183).

endocarditis malignant malaria and primary aplastic anaemia. Haemoglobin was reduced to 20 per cent and red corpuscles to less than one million while white corpuscles numbered 15 000 per cubic millimetre. Death occurred in October about 3 months from the onset of symptoms. Necropsy showed a soft ulcerated carcinoma 3 centimetres in diameter on the posterior wall of the pyloric antrum with soft haemorrhagic deposits in many abdominal and mediastinal lymph glands and extensive ill defined areas of metastatic growth in many bones. No other organs contained obvious growths but there were widespread petechial and larger haemorrhages in many tissues. Microscopy—Different parts of the tumours in the stomach lymph glands and bones showed mucoid adenocarcinoma spheroidal and signet ring cell carcinoma and anaplastic cellular growth. The small blood vessels and lymphatics of the lungs showed widespread tumour infiltration accompanied by haemorrhage.

(d) Other metastases

No organ or tissue is exempt from blood borne metastases from gastric carcinoma. They are not uncommon in the adrenals kidneys and myocardium they are unusual in the thyroid brain meninges and skin and are rare in other tissues (Willis 1934). Senge saw metastases in the placenta. The secondary growths in the breasts described by Stahr and by Dawson probably arrived by way of lymphatic paths and the same may apply to some deposits in the meninges as in the cases of Knerim and Cornwall. In other cases however, meningeal dissemination is secondary to a metastasis in the brain as in Duncan's case.

REFERENCES

- Achard C, Bari  ty M, Desbuquois G and Sternfeld (1931) *Bull Soc med H  p Paris* 55 184
 Aird I (1935) *Brit J Surg* 22 545
 Bonne C *et al* (1938) *Amer J Cancer* 33 265
 Castleman B (1936) *Ann Surg* 103 746
 Chaplin A (1913) *The Illness and Death of Napoleon Bonaparte* London
 Cornwall L H (1927) *Arch Neurol Psych* 17 466
 Craver L F (1932) *Amer J Cancer* 16 68
 Davis C L and Naylor J R (1943) *J Amer Vet Med Assoc* 102 286
 Dawson E K (1936) *J Path Bact* 43 53
 DIBLE J H (1925) Gastric ulcer and gastric carcinoma: an enquiry into their relationship *Brit J Surg* 12 666 (A careful study with many excellent illustrations)
 Duncan C A (1941) *Med J Austral* 5 541
 Funk E H and Crawford B L (1923) *N Y Med J* 118 101
 Gaertner K (1938) *Frankfurt Z Path* 52 1
 Gauthier Villars P (1928) *Ann Anat path* 5 1
 Glockner A (1904) *Arch Gynak* 72 410
 Gloor W (1929) *Schweiz Med Wschr* 59 151
 Guiss L W and Stewart F W (1943) *Arch Surg* 46 823
 Harrington A W and Teacher I H (1910) *Glasgow Med J* 73 241
 Harrington A W and Kennedy A M (1913) *Lancet* 1 378
 Hauser G (1895) *Virchows Arch* 141 485
 Hebbel R (1943) *Amer J Path* 19 43
 Herbert W E and Bruske J S (1936) *Guy s Hosp Rep* 86 301
 Hurst A F (1929) *Lancet* 1 1023
 Kaplan H S and Rugler L G (1945) *Amer J Med Sci* 209 339
 Kaufmann E (1929) *Pathology* p 695 (Reimann's translation) Philadelphia
 Kirby A H M (1944) *Cancer Res* 4 94
 Kirby A H M (1945) *Ibid* 5 129
 Knerim G (1908) *Beitr path Anat* 44 409
 KONJETZNY G E (1938) *Der Magenkrebs* Stuttgart (An admirable monograph with full bibliography and many excellent photographs and photomicrographs)

adenocarcinomatous and signet ring-cell structure are seen. The kind of gastric growth usually responsible for Krukenberg tumours is the diffusely infiltrating spheroidal cell or signet ring cell carcinoma. The primary growth is often small and relatively symptomless, the large ovarian tumours giving the first or main signs of disease. Skiagrams of the stomach may fail to disclose any abnormality, and even at necropsy a small diffuse primary growth may escape detection. Hence the necessity for adopting very strict criteria before accepting supposed cases of 'primary' Krukenberg tumours of the ovary. Apart from secondary deposits in the perigastric lymph glands and sometimes in the peritoneum Krukenberg tumours are often unaccompanied by metastases in other organs. Especially notable is the frequent escape of the liver.

(4) Metastasis by the blood stream

(a) *The liver*

The liver contains discrete metastases in a high proportion (at least one third) of fatal cases: e.g. in 33 per cent of Kaufmann's Basle cases, in 36 per cent of Poscharissky's and in 46 per cent of my 85 cases. These clearly arise by embolism following invasion of main tributaries of the portal vein (Willis 1930).

(b) *The lungs*

The lungs show secondary growths in about one quarter of fatal cases: e.g. in 19 of my 85 cases. In 14 of these 19 cases the pulmonary growths were discrete and clearly blood borne; in the other 5 cases there was widespread permeation of peribronchial and subpleural lymph vessels with some nodulation (Fig. 183) and it was uncertain whether the growths had reached the lungs by the bloodstream or by retrograde lymphatic spread from affected hilar lymph glands. In 4 additional cases tumour emboli were found microscopically in the arterioles of lungs which showed no visible growths to the naked eye. The difficulty just mentioned of distinguishing between haemic metastasis followed by lymphatic permeation in the lungs and nodular lymphatic spread from hilar deposits, must arise in many cases of 'miliary' carcinosis of the lungs secondary to gastric cancer, a condition with which pathologists have long been familiar and which is now well recognized by radiologists also as sometimes producing skiagrams as well as naked eye appearances, suggesting miliary tuberculosis (Funk and Crawford, Gloor, Achard *et al.*).

(c) *Bones*

Bones contain metastases in between 5 and 10 per cent of fatal cases. Occasionally, these produce serious local results such as tumour or pathological fracture, which may simulate primary skeletal disease as in cases described by Konjetzny and myself (1938). In an important group of cases widespread metastases in bone marrow often from small relatively symptomless primary growths seriously affect haemopoiesis and produce severe megalocytic anaemia or thrombocytopenia (Harrington and Teacher, Harrington and Kennedy, Seeman and Krasnopolski, Laurence and Mahoney, other references by Willis 1934 pp. 324 and 342-4, and the following case).

Case 11—History.—In July 1943 a man aged 36 who had been on active service in the tropics began to suffer from weakness, pyrexia and pallor. These symptoms became rapidly worse and diagnoses made during ensuing weeks included acute bacterial

CHAPTER 22

EPITHELIAL TUMOURS OF THE SMALL INTESTINE

EPITHELIAL tumours of the small intestine are much less common than those of the stomach or large intestine. My necropsies include 17 cases of carcinoma of the small intestine, as against 227 of the stomach and 190 of the large intestine. These were briefly as follow:

SUMMARY OF 17 NECROPSY CASES OF CARCINOMA OF THE SMALL INTESTINE

Case No	Sex age	No. and sites of tumours	Histology	Metastases
I	M 66	3 ileum	Argentaffin carcinoma	None
II	M 77	Many throughout	Argentaffin carcinoma	None
III	M 37	Single ileum	Argentaffin carcinoma	Lymph glands liver
IV	M 67	Single ileum	Argentaffin carcinoma	Lymph glands kidney
V	M 56	Many throughout	Argentaffin carcinoma	In many organs
VI	M 41	Many jejunum	Argentaffin carcinoma	Brain and other parts
VII	M 68	7 ileum	Argentaffin carcinoma	None
VIII	F 70	Many ileum	Argentaffin carcinoma	None
IX	M 25	Single upper jejunum	Anaplastic carcinoma	Lymph glands
X	M 44	Single duodenum	Adenocarcinoma	Lymph glands thoracic duct lungs
XI	F, 70	Single upper jejunum	Adenocarcinoma	Lymph glands liver, peritoneum
XII	F 72	Single duodenum	Adenocarcinoma	None
XIII	M 62	Single upper jejunum	Adenocarcinoma	Lymph glands
XIV	M 71	Single duodenum	Adenocarcinoma	Lymph glands
XV	F 50	Single duodenum	Adenocarcinoma	Lymph glands liver lungs
XVI	F 53	2 duodenum and upper jejunum	Anaplastic carcinoma	Lymph glands liver lungs adrenal
XVII	F 63	Single upper jejunum	Adenocarcinoma	Lymph glands thoracic duct lungs liver ovary

Nos. I to VI and IX to XII have been described elsewhere (Willis, 1940 and 1941).

I shall describe enteric epithelial tumours under the following heads:

- (1) Benign tumours of the small intestine
- (2) Non argentaffin carcinomas of the small intestine
- (3) Argentaffin carcinomas of the small intestine
- (4) Tumours of vitello intestinal structures
 - (a) of Meckel's diverticulum
 - (b) of the umbilicus

BENIGN TUMOURS OF THE SMALL INTESTINE

These are very rare. In my necropsy work I have not encountered any papillary or adenomatous polyp comparable with those of the stomach or large intestine.

- Krukenberg F (1895) *Arch Gynak* 50 287
- Laird D A (1921) *Fdnb Med J* 26 98
- Laurence J S and Mahoney E B (1934) *Amer J Path* 10 383
- Lantott G A M (1936) *Guy's Hosp Rep* 86 293
- Major R H (1918) *Surg Gyn Obst* 27 195
- Mallory T B (1940) *Arch Path* 30 348
- Miller T G Eliason E L and Wright V W M (1930) *Arch Int Med* 46 841
- Moore N (1885) *Trans Path Soc Lond* 36 195
- Ness R B and Teacher J H (1908) *Brit J Child Dis* 5 515
- Nettleship A (1943) *Arch Surg* 46 793
- NEWCOMB W D (1933) The relationship between peptic ulceration and gastric carcinoma *Brit J Surg* 20 279 (An excellent study and review)
- Nicholson G W (1923) *Guy's Hosp Rep* 73 37
- Orator V (1925) *Virchows Arch* 256 202
- Pack G T and Le Fevre R G (1930) *J Cancer Res*, 14 167
- Fain A B (1934) *Brit J Surg* 21 542
- PEACOCK, P R (1943) Gastric cancer: an experimental approach to the problem of causation *Glasgow Med J* 139 117 (An admirable outline of the problem)
- Poscharissky T (1930) *Z Krebsforsch* 31 263
- Quenu and Longuet (1896) *Rev Chir* 16 97
- Rigler L G Kaplan H S and Fink D L (1945) *J Amer Med Assoc* 128 426
- Rissel W (1907) *Beitr path Anat* 42 233
- Rudduck H B and Willis R A (1938) *Amer J Cancer* 33 205
- Schiurge M (1922) *Virchows Arch* 237 129
- Schmucker K (1928) *Virchows Arch* 267 339
- Schneider P J (1940) *Amer J Cancer* 38 263
- Seemann G and Krasnopolski A (1926) *Virchows Arch* 262 697
- Senge J (1912) *Beitr path Anat* 53 532
- Shaw W (1925) *Proc Roy Soc Med (Sec Obst Gyn)* 19 49
- Sokoloff B (1938) *Amer J Surg* 40 673
- SPRIGGS, E I (1943) Polyps of the stomach and polypoid gastritis *Quart J Med* 12 1 (A valuable account with an historical outline many references and good illustrations)
- Stahr H (1923) *Z Krebsforsch* 19 231
- Stewart M J (1913) *J Path Bact* 17 409
- Stewart M J (1926) *Ibid* 29 321
- Stewart M J (1929) *Brit Med J* ii 567
- STEWART M J (1931) *Precancerous Lesions of the Alimentary Tract* Reprinted from *Lancet* ii 565 617 and 669 (Epitomizes the author's own extensive studies and critically reviews many other writers)
- Stewart M J and Taylor A L (1925) *J Path Bact* 28 195
- Stone W S (1916) *Surg Gyn Obst* 22 407
- Stout A P (1943) *Arch Surg* 46 807
- Troisier E (1889) *Arch gen méd* 1 129 and 297
- Tsunoda T (1910) *Z Krebsforsch* 9 436
- Versé M A *References* Chapter 7
- Walters W Gray H K and Priestley J T (1943) *Arch Surg* 46 939
- Wanser R (1939) *Beitr path Anat* 103 113
- Washburn R N and Rozendaal H M (1938) *Ann Int Med* 11 2172
- WELLS H C SLAYE, M and HOLMES H F (1938) Comparative pathology of cancer of the alimentary canal with report of cases in mice *Amer J Cancer* 33 223 (A valuable review)
- WILKINSON J F (1933) Diseases associated with pernicious anaemia (in a study of 370 cases) *Quart J Med* 2 281 (An outline of the writer's own experience and a valuable review)
- WILKINSON J F (1945) *Brit Med J* ii 664 (Wilkinson summarizes his findings to date)
- Willis R A (1930) *J Path Bact* 33 849
- WILLIS R A (1934) *The Spread of Tumours in the Human Body* London
- Willis R A (1941) *Med J Austral* ii 258

relationship is very doubtful. Reports of enteric carcinoma coexisting with tuberculous enteritis, syphilis or other infections are too few to be significant.

(5) Metastases

These are found in the neighbouring lymph glands or in the liver in more than one-half of fatal cases, but metastases in lungs and other organs are infrequent. My Case X showed invasion of the thoracic duct with resulting profuse embolic dissemination to the lungs (Fig. 47), and in Case XVII the thoracic duct was occupied by tumour right up to its cervical exit from which a polypoid mass of growth projected into the great veins, and there were multiple metastases in the lungs, as well as in the liver and right ovary.

ARGENTAFFIN CARCINOMAS OF THE SMALL INTESTINE

These tumours are still insufficiently known to pathologists and surgeons. They occur nearly as frequently as the adenocarcinomas just described, e.g. in

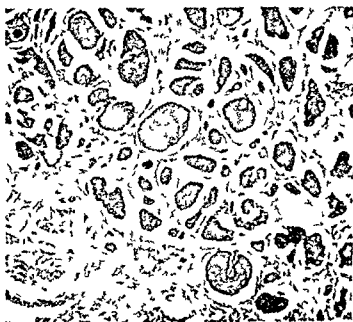


FIG. 184—Typical structure of argentaffin carcinoma ($\times 55$)

8 of my 17 necropsy cases of enteric carcinoma and in 30 of 130 cases of tumours of the small bowel in Dockerty and Ashburn's series. For other good accounts of these growths see Cope and Newcomb, Cooke, Marangos, Humphreys, Ariel Willis (1940) and Dangremond.

(1) Nomenclature and histogenesis

The frequently used name 'carcinoid tumour', introduced by Oberndorfer in 1907, is an unfortunate one, implying a reputation of innocence which later experience has shown to be undeserved. Many 'carcinoids', of the small intestine especially, are dangerously invasive and metastasizing growths. They should be called argentaffin or Kulchitzky cell carcinomas, since there is clear

Baggenstoss refers to some reported cases, and records 25 examples of small polypi 2 to 5 millimetres in diameter situated on the duodenal papilla. Feyrter describes several specimens of nodular hyperplasia or circumscribed adenoma of Brunner's glands.

NON ARGENTAFFIN CARCINOMAS OF THE SMALL INTESTINE

Adenocarcinomas of ordinary structure and of varying degree of differentiation are the commonest tumours of the small intestine. These appear as annular stenosing ulcerated or polypoid growths and usually cause intestinal obstruction.

(1) Site

The most frequent sites are the second part of the duodenum and the upper part of the jejunum. Hoffman and Pack recorded that of 228 carcinomas of the small intestine 104 arose in the duodenum. Duodenal carcinoma has been well described by Meyer and Rosenberg, Rutishauser, Hoffman and Pack, Stewart and Lieber, Lieber *et al* and Baggenstoss. It arises most frequently in or near the papilla of Vater and it is often difficult to decide whether the tumour is ampullary or duodenal in origin. In advanced cases it is often impossible also to distinguish a duodenal from a pancreatic carcinoma. Beyond the duodenum the favourite site of enteric carcinoma is in the first two feet of the jejunum where the growth is usually of tightly stenosing annular form. Of 6 surgically resected specimens which I have examined 4 were from the upper part of the jejunum. Adenocarcinomas of the ileum are rare, those of the ileo caecal orifice are more often caecal than ileal.

(2) Age incidence

This is similar to that of gastro intestinal carcinoma in general. The mean age of the combined series of patients with duodenal carcinoma cited above was 55 years and that of my 9 necropsy cases 57 years. The lowest age recorded is 16 years.

(3) Sex incidence

Men are affected more than women especially from duodenal carcinoma the sex ratio being about 2 to 1 in most series. Of my 7 upper jejunal carcinomas—3 necropsy and 4 surgical specimens—5 were from women.

(4) Antecedent lesions

These have rarely been seen. Meyer and Rosenberg and Konjetzny (1938 p. 120) have referred to cases of duodenal cancer supposed to have supervened on chronic ulcer but these are exceptional some of them are dubious, and in some others coexistence of the two lesions may have been fortuitous. It is notable that duodenal carcinoma develops much more frequently in the periampullary region than in the first part of the organ where most ulcers occur. Stewart and Lieber found no evidence of previous chronic ulcer in their 6 cases of supra papillary carcinoma. Gall stones are recorded in a small proportion of cases of periampullary cancer e.g. in 5 of 28 cases (Baggenstoss), but a causative

necropsy cases 2 showed solitary tumours, one showed 3 tumours and 5 showed many tumours. Cooke found them recorded as multiple in 27 of 76 cases, but these included surgically removed as well as necropsy specimens. Visible multiple growths often number 20, 40, 60 or more, but in addition to the visible ones the mucosa often contains many tiny tumour foci which are disclosed only by microscopical search. The ileum is usually more affected than the jejunum, but in my Case VI there were visibly multiple tumours in the jejunum only. Multiple enteric growths may be accompanied by tumours in the stomach or pancreas, and it may prove difficult to decide whether these are metastases or truly multiple growths (Willis, 1940).

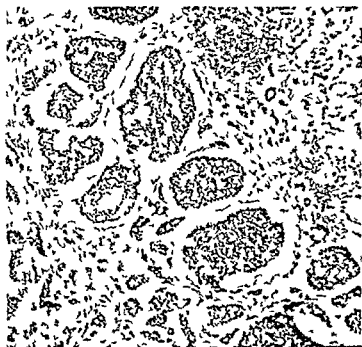


FIG 186—Typical structure of argentaffin carcinoma in a metastasis in the liver ($\times 90$)

Young tumours usually take the form of nodules or plaques projecting into the bowel lumen and covered by intact mucosa. As they enlarge they often show central umbilication or ulceration. Older growths, especially solitary ones, may encircle the bowel and cause infolding of the muscle coat and stenosis, well depicted by Humphreys. Microscopical study reveals that even small seemingly well defined tumours have often sent fine extensions into the muscular and serous coats (Fig 185), as this infiltration extends, it may cause dense fibrosis of the tissues, and may be accompanied also by apparent hyperplasia of the invaded muscular tissues. The yellow colour of the tumours is retained in all these situations, and often in metastases also.

(3) Age and sex incidence

The tumours are found chiefly during middle or old age. The mean age of my 8 necropsy cases was 60 years, of Dockerty and Ashburn's 13 cases with metastases

evidence that they arise from the specialized granular epithelial cells of the crypts of Lieberkuhn, the yellow cells of Kultschitzky later shown by Masson to have selective argentaffin staining properties. The tumour cells show silver stainable granules like those of the Kultschitzky cells, and the cut surface of the tumours, like the cells from which they arise, often show a characteristic yellow or orange colour. In most cases these carcinomas are histologically so distinctive that they can be identified readily without using the somewhat fickle silver staining test (Figs 184-186). They typically consist of well defined solid clumps or strands of rather small closely packed polyhedral cells with here and there small glandular

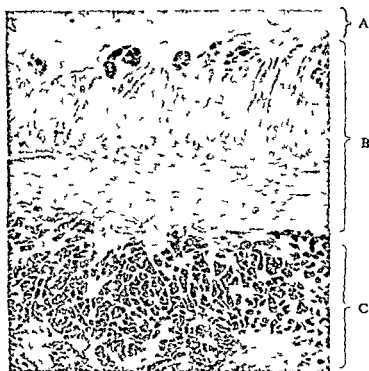


FIG 185—Microscopic degree of infiltration by argentaffin carcinoma to outer coats of bowel. A = serosa B = muscularis C = main mass of growth in submucosa ($\times 32$)

lumina or distinct acini. The more actively growing tumours show varying degrees of anaplasia in part or whole (Figs 187, 188), so that they may escape immediate histological recognition (as in Case V, Willis 1940).

The causation of argentaffin carcinomas is quite unknown and is likely to remain so until we discover the functions of the argentaffin cells. The frequent multiplicity of the tumours in the intestine shows that, whatever the carcinogenic factors may be they operate over the whole mucosa of the small bowel. In accordance with the presence of some argentaffin cells in the stomach, colon, pancreas and gall bladder occasional argentaffin carcinomas in these organs have also been described (Ashworth and Wallace) and they occur too in Meckel's diverticulum (*see below*).

(2) Number, site and appearance

Argentaffin carcinomas of the small intestine are often multiple. Of my 8

composed of gastric and Brunner's glands in a Meckel's diverticulum in a boy aged 16 years and were able to find records of only 3 other adenomas in diverticula. *Argentaffin carcinoma* is the most frequent kind of neoplasm of Meckel's diverticulum (Stewart and Taylor, Price, Ashworth and Wallace)

(2) Umbilicus

Umbilical polypi, sinuses or cysts lined by intestinal or gastric epithelium derived from the vitello intestinal duct are not very rare (Nicholson, Petersen). I have examined an umbilical cyst 1.5 centimetres in diameter lined by gastric mucosa from a boy aged 2 years, and an extroverted polypus clothed by gastric mucosa, from a boy of 3 years, both present since birth, a collection of inflamed cysts 2 centimetres in total diameter, lined by columnar intestinal epithelium from a woman of 30 years and a cystic papillary tumour, probably of urachal origin (Case VI, Chapter 28)

REFERENCES

- Ariel I M (1939) *Arch Path* 27 25
 Ashworth C T and Wallace S A (1941) *Arch Path* 32 272
 Baggenstoss A H (1938) *Arch Path* 26 853
 COOKE, H H (1931) Carcinoid tumors of the small intestine, *Arch Surg* 22 568
 (A good description of 11 cases and a useful review)
 Cope Z and Newcomb W D (1930) *Brit J Urol* 2 268
 Dangremond G (1942) *Amer J Clin Path* 12 223
 Dockerty M B and Ashburn F S (1943) *Arch Surg* 47, 221
 Fevrer F (1934) *Virchows Arch* 293 509
 HOFFMAN, W J, and PACK, G T (1937) Cancer of the duodenum, *Arch Surg* 35 11
 (A good account of 18 cases)
 Humphreys E M (1934) *Amer J Cancer* 22 765
 Konjetzny G E (1938) *Der Magenkrebs* Stuttgart
 Lieber, M M Stewart H L and Lund H (1937) *Arch Surg* 35 268
 Marangos G N (1931) *Beitr path Anat* 86 48
 Meyer J and Rosenberg D H (1931) *Arch Int Med* 47 917
 Nicholson, G W (1923) *J Path Bact* 26 399
 Petersen W W (1939) *Virchows Arch* 303 234
 Price I (1935) *Brit J Surg* 23 30
 Rutishauser E (1932) *Frankfurt Z Path* 43 133
 Schullinger R N and Stout A P (1934) *Arch Surg* 28 440
 Stewart H L and Lieber M M (1937) *Arch Surg* 35 99
 Stewart M J and Taylor A I (1926) *J Path Bact* 29 135
 WILLIS R A (1940) Argentaffin carcinomata (Carcinoids) of the small intestine
Med J Austral 11 400 (Details of 6 necropsy cases and discussion of malignancy and metastasis)
 Willis R A (1941) *Med J Austral*, 11 258

58 and of the cases reviewed by Ariel 57 Males predominate Cooke's and Ariel's combined figures comprised 100 men and 73 women, Dockerty and Ashburn's series comprised 8 men and 5 women, and 7 of my 8 necropsy cases were men

(4) Spread and metastasis

Following infiltration of the bowel wall spread in the peritoneum may lead to fibrotic contraction and kinking of the gut Metastasis to the neighbouring

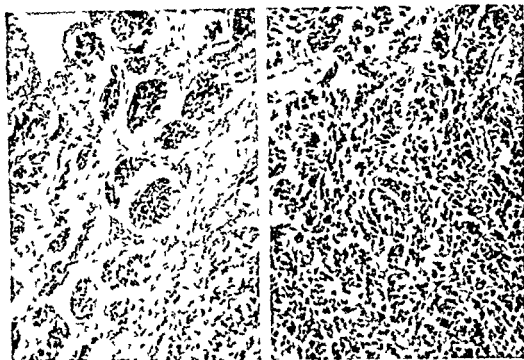


FIG 187—Case I Slightly anaplastic structure in a metastasis of argentaffin carcinoma in a lymph gland ($\times 105$)

FIG 188—Case I Markedly anaplastic structure in a primary intestinal argentaffin carcinoma ($\times 105$)

mesenteric lymph glands or to the liver frequently takes place (Figs 186 187) Occasionally more remote metastases also appear e.g. in my Case V above, in the lungs kidneys adrenals retroperitoneal tissue subcutaneous tissue and perhaps in the gall bladder stomach and pancreas (but these were possibly the sites of independent primary growths), in the brain skin and possibly in the pancreas, in Case VI and in the kidney in Case IV Peritoneal dissemination is not common but was seen in the remarkable case described by Cope and Newcomb For other instances of metastasis see the papers already cited and other references in my 1934 work (pp 128 9)

TUMOURS OF VITELLO INTESTINAL TISSUES

(1) Meckel's diverticulum

Adenomas are very rare Schullinger and Stout saw a pedunculated adenoma

331 operation specimens, Dukes found the right sided parts of the colon affected in 75 and the left sided parts in 256, while during the same period there were more than 1 000 cases of rectal cancer. Raiford's series comprised 319 cancers of the rectum and 192 cancers of the colon, the latter including 67 of the caecum and ascending colon and 72 of the descending or sigmoid colon. The transverse colon and the hepatic and splenic flexures are the least common sites.

(5) Multiple carcinomas

Multiple carcinomas of the large intestine may occur in the same segment or in widely separated parts of the bowel (Norbury Gordon Taylor, Dukes). My necropsies included, in addition to Cases I, II and IV, the following combinations of sites of multiple growths in which the possibility of spread or metastasis from one site to the other could be excluded: (i) caecum and sigmoid,



FIG 189—Adenocarcinoma of colon in a rat ($\times 50$)

- (ii) hepatic flexure, splenic flexure and descending colon (plus multiple polyp),
 - (iii) 3 separate carcinomas (and a polypus) in the sigmoid, (iv) sigmoid and rectum.
- Dukes found multiple foci of origin in 29 of 1,000 cases of rectal carcinoma.

(6) Intestinal carcinoma in animals

Like gastric cancer, intestinal cancer is rare in all mammals except man. Wells *et al* (1938) have reviewed the few reported examples in the mouse, rat, cat, dog, lion, ox, horse, racoon and dasyure, as well as the more frequent reports of the disease in birds. Intestinal carcinoma in mice occurs mainly in the prolapsed rectum and is more often squamous celled than adenocarcinoma. In 1935, I described two mucoid adenocarcinomas of the colon in rats, with metastases in lymph glands in both cases (Fig 189). Schlotthauer reported a mucoid

CHAPTER 23

CARCINOMA OF THE LARGE INTESTINE

THE MAIN subject of this chapter is the common adenocarcinoma. Benign epithelial tumours are considered in relation to cancer, and tumours of the appendix and anus are described separately in the last sections.

FREQUENCY AGE SEX SITE AND SPECIES INCIDENCE

(1) Frequency

In Great Britain, Australia and some other countries mortality and hospital statistics show that carcinoma of the large bowel is only a little less frequent than carcinoma of the stomach. Thus, in Victoria in 1940-42 1,534 deaths from cancer of the intestines were recorded as against 1,720 from cancer of the stomach and my proved necropsy cases included 190 of carcinoma of the large intestine and 227 of carcinoma of the stomach. In communities where gastric cancer (qv) is unusually frequent, intestinal cancer accounts for a correspondingly lower proportion of all cancers, though it is still one of the commonest tumours in most countries.

(2) Age

The greatest number of patients is in the sixth decade. The mean age in Hayden and Shedden's series of rectal cancers was 57 for men and 49 for women and in Dukes's (1940) series of 1,000 rectal cancers 59 for men and 55 for women. The mean age of my 190 necropsy cases was 60. The disease is rare under 30 years of age but has been seen in children e.g. in a boy of 16 years by Willis (1934) in a boy of 13 years by Ogilvie, and in a girl of 9 by Webster, who gives other references. Carcinoma supervening on familial polyposis often occurs in the second, third or fourth decades. My second youngest necropsy case, a male of 24 years, was of this kind (see Case I below).

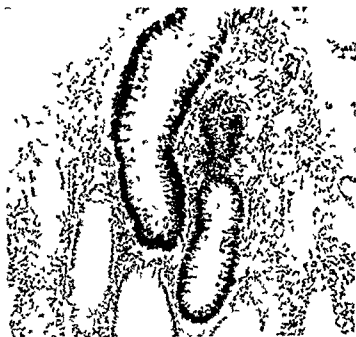
(3) Sex

Men are more often affected than women in a proportion between 3:2 and 2:1 in most series, e.g. 114 men and 76 women in my necropsy series. In Raiford's series the sex ratio was 2:1 for colonic cancer and nearly 3:1 for rectal cancer. The 1,000 rectal carcinomas recorded by Dukes were from 650 men and 350 women. Hayden and Shedden's cases of rectal cancer comprised 179 men and 124 women. Dukes (1945) points out that cancer of the proximal end of the colon is more common in women than in men but that cancer of the pelvic colon and rectum is much commoner in men than in women.

(4) Site

Carcinoma increases in frequency from the proximal to the distal parts of the large intestine the rectum being the most frequent site of all. In a series of

Case II—History—A woman aged 50 years had had intermittent diarrhoea for 30 years the motions usually being fluid and sometimes streaked with blood. Following recent attacks of abdominal colic and vomiting sigmoidoscopy had revealed polyposis and a fungating carcinoma of the upper rectum. *Necropsy* showed multiple polyposis of the entire large intestine a large fungating carcinoma of the ileo-caecal orifice a fungating carcinoma 3 centimetres in diameter of the recto sigmoid junction and an indefinite area suggesting carcinoma in the transverse colon sections of which confirmed the presence of early adenocarcinoma extending into the muscle coat. No metastases were found.



FIGS 190 and 191—*Case I* Polyposis of colon showing multiple tumour foci in which the glands show cellular atypism and hyperchromatism ($\times 20$ and 120)

(b) *Carcinoma is often accompanied by polyp*

This was so in 27 per cent of 79 necropsy cases examined by Stewart (1931) and in no less than 25 of 33 consecutive cases of rectal and sigmoid carcinoma examined by Dukes (1926). In a consecutive series of 40 operation and necropsy

adenocarcinoma of the rectum with lymph nodal and omental metastases in a dog

CAUSATIVE FACTORS

(1) Intestinal polypi

The structure of the common intestinal polypi—papillomas and adenomas—is too well known to require description. They consist of well differentiated glandular tissue like that of the colonic mucosa with however, varying degrees of distortion of the epithelium and crowding and hyperchromatism of the nuclei. Early tumours appear as small sessile nodules, larger ones develop strap like pedicles clothed by normal mucosa. The tumours may be solitary, few many or innumerable. The rectum and pelvic colon are the commonest sites of solitary or few polypi and are often the most heavily affected parts in cases with many growths. Patients with very numerous tumours—multiple polyposis—often give a family history of the disease, many examples of familial polyposis were recorded by Dukes (1930) and Lockhart Mummery and Dukes (1939). The disease may arise in several successive generations may be transmitted by either sex and affects males and females about equally. The polypi are not congenital but usually commence to appear between the ages of 15 and 25 years. What is inherited is therefore not polyposis as such but a special proneness of the colonic mucosa to neoplasia. No family tendency is apparent in cases with solitary or few polypi and these may develop at any age.

All polypi of the large intestine—whether numerous few or single and whether familial or not—are predisposed to carcinomatous change the predisposition being least in the solitary polypus and greatest in familial polyposis. Let us consider the evidence under three heads

(a) *Familial polyposis terminates in cancer*

Victims of familial polyposis are almost certain to die of carcinoma of the colon or rectum at an early age usually between 25 and 45 years. Dukes and Lockhart Mummery recorded many instances and the following case exemplifies the early development of carcinoma

Case 1—History—Patient's mother died of intestinal carcinoma following polyposis his maternal grandfather died of diarrhoea his only sister had proved polyposis and was probably developing carcinoma when last heard of his only brother was healthy. At the age of 10 years the patient began to suffer from diarrhoea which was at first attributed to colitis but later shown by skiagrams and sigmoidoscope to be due to polyposis. This became steadily worse some clubbing of the fingers developed and he died at the age of 24. *Autopsy* showed severe polyposis of the whole large intestine 4 separate areas of ulcerated carcinoma in the rectum the largest 3 centimetres in diameter metastases in neighbouring glands and peritoneum many large metastases in the liver (3 860 grammes). *Microscopy* showed active anaplastic adenocarcinoma and also revealed innumerable tiny foci of adenoma or early adenocarcinoma in many parts of the colonic mucosa. (See Figs 190 and 191 and compare with Lahm's.)

Not all cases of widespread polyposis are familial. The following is an example of this disease terminating in multiple carcinoma in which there was no record of any family tendency

It should be added that the "polypi" often mentioned in ulcerative colitis are usually not true neoplastic polypi, but merely inflammatory polypoid projections of residual mucous membrane

(b) *Diverticulosis or diverticulitis*

This sometimes coexists with carcinoma (references by Stewart, 1931), but it is probable that the association is wholly fortuitous. Diverticulosis of the distal part of the large intestine is common in elderly subjects, so that its coexistence with cancer is inevitable in a considerable proportion of cases

(c) *Other intestinal infections*

Amoebic and bacillary dysentery, tuberculosis, bilharziasis, etc., apparently do not predispose to cancer. In Egypt rectal cancer is infrequent despite the prevalence of bilharzial disease (Dolbey and Mooro, 1924)

(3) *The possible presence of ingested carcinogens*

Possible sources of ingested carcinogenic substances have been discussed in Chapter 21 and it was suggested that if these are poorly absorbable they might be an effective cause of colonic cancer. Dukes (1945) made a similar suggestion.

If cancer of the colon is due to a carcinogenic agent present in the faeces its influence would certainly be greatest towards the distal end of the colon because of the slower passage and greater concentration of the intestinal contents. Perhaps future research will succeed in identifying carcinogenic substances in the faeces

THE STRUCTURE AND GROWTH OF CARCINOMA

As in the stomach so in the bowel, carcinoma may assume predominantly polypoid, ulcerative stenotic or diffuse forms. Microscopically most tumours are adenocarcinomas, often of well-differentiated columnar cell type, often too of papillary pattern and often mucus secreting. Diffusely infiltrating spheroidal-cell or signet ring cell tumours are uncommon. So also are very anaplastic growths devoid of glandular orientation of the cells. Squamous metaplasia is rare. Excluding the appendix (*see below*), the large intestine is a rare site of argentaffin carcinoma (Stout, Ashworth and Wallace, Potter and Docter). It is possible that the tumour in Case III above was of this kind.

Polypoid carcinomas often attain a large bulk within the bowel while effecting only slight infiltration of the wall. Infiltrating and stenosing growths, however, soon extend through the muscle coats and invade the surrounding peritoneal and fatty tissues. Here veins are often invaded. Invasion of veins was demonstrated in 17 per cent of the surgical specimens of rectal cancer studied by Dukes (1940, 1944) and in 70 of 170 necropsy cases of rectal cancer studied by Brown and Warren. It is demonstrable rather less frequently with colonic growths.

Osseous metaplasia of the stroma occurs rarely in intestinal carcinoma (Dukes, 1939).

specimens of carcinoma of the large bowel which I examined carefully for polypi, these were found in 24 they were multiple in 18 and were usually in the neighbourhood of the main growth. These findings show that intestinal carcinoma commonly arises in a field of predisposed mucosa. 'A crop of adenomata arise from this sensitive field' (Dukes). The extent of the potentially neoplastic field evidently varies greatly it may be restricted to a local segment, or it may involve the whole large intestine as in widespread polyposis.

(c) *Carcinomatous change in progress in a polypus is sometimes observed*

Swinton and Warren concluded that an origin from polypi was demonstrable in 14 per cent of 827 cases of colonic and rectal carcinoma. I have seen carcinomatous change develop in a polypus which presented in the sigmoid colostomy opening of a patient with inoperable carcinoma of the rectum. The following case showing carcinoma of a polypus very clearly, has other points of interest also.

Case III—A woman of 46 years died of abdominal malignant disease of clinically undetermined origin the chief symptoms of which had been recent rapid enlargement of the liver, jaundice and emaciation. *Necropsy*—The sigmoid colon contained a polypus 1.5 centimetres in diameter with a narrow pedicle clothed by normal mucous membrane and a crateriform ulcer 1 centimetre in diameter on its summit. The meso-colon close to the base of the pedicle contained a mass of secondary growth in lymph glands 2.5 centimetres in diameter. The liver weighed 9 pounds and contained many large metastatic tumours and deposits were present in the portal and mesenteric lymph glands. The mucous membrane at the fundus of the gall bladder contained a nodule of tumour 1 centimetre in diameter. Small scattered nodules of growth were present in the pancreas and spleen. The cranial dura mater presented 2 tumour nodules each 1 centimetre in diameter. Many soft destructive areas of growth were present in the skull ribs and vertebrae. *Microscopy*—In all situations the tumours were anaplastic, spheroidal-cell growths with only slight suggestions of glandular formation. The structure somewhat recalled that of anaplastic argentaffin carcinoma but this diagnosis could not be claimed with certainty.

(2) Inflammatory diseases

(a) *Ulcerative colitis*

This condition is occasionally followed by carcinoma. Thus carcinoma developed in 2.5 per cent of Brust and Bergen's 800 cases of colitis, but whether this proportion significantly exceeds that to be expected fortuitously is not clear from their paper since this gave no details of the age distribution of their cases. They mentioned however that carcinoma supervening on colitis was often found in relatively young patients. The following is the only example of this association that I have seen in about 30 necropsies on cases of ulcerative colitis.

Case II—A man of 42 years died after having been under hospital treatment for ulcerative colitis for many years. He had been treated with Bergen's vaccine and had had a long period with good health prior to the onset of the fatal illness. *Necropsy* showed severe ulcerative inflammation throughout the large intestine, an ulcerated carcinoma 4 centimetres in diameter in the sigmoid colon and a separate stenosing carcinoma in the rectum. *Microscopy* showed both tumours to be adenocarcinomas involving all coats and accompanied by deposits in neighbouring lymph glands. A section of the colon in another part unexpectedly revealed a third area of early adenocarcinoma invading the muscle.

119 ounces Case III above exemplifies massive hepatic metastasis from a very small primary growth

(b) *The lungs*

The lungs contain secondary growths in about one fifth of fatal cases

(c) *Other organs*

Other organs, most often the adrenals, kidneys or bones, are affected in about 10 per cent of cases (Brown and Warren, Willis, 1941)

CARCINOMA OF THE APPENDIX

In 1906 Rolleston and Jones accepted and reviewed 42 previously reported cases of primary cancer of the appendix. They found these to be of two distinct types—the columnar celled like that of the large intestine and the spheroidal-celled, the latter being the tumour later designated “carcinoid” or argentaffin carcinoma. Uihlein and McDonold distinguished three kinds of appendical cancer—the ‘carcinoid’ type, the cystic type producing pseudomyxoma peritonei, and the colonic type—and estimated the relative frequencies as 89, 8 and 3 per cent respectively. It is, however, debatable whether the appendical lesion responsible for pseudomyxoma is usually truly neoplastic or only an obstructive mucocele. I have discussed this question, with references, elsewhere (Willis, 1934). Here we will consider only the two undoubted types of carcinoma of the appendix, argentaffin carcinoma and adenocarcinoma of colonic type.

(1) Argentaffin carcinoma

This is by far the commonest tumour of the appendix. It is most often situated at or near the tip, and appears as a hard mass of yellowish tissue usually only 1 or 2 centimetres in diameter which may appear well defined or may infiltrate the appendical wall without clear demarcation. Partial calcification of the growth occasionally occurs. Most of the tumours are discovered only incidentally at operations for appendicitis or at necropsy. In their number, and their age and sex incidence they differ from the similar tumours of the small intestine (q.v.). The appendical tumours are usually single, only rarely multiple. They are discovered at ages ranging from 12 to 70 years, but most of them are found during the second and third decades—the average age of the cases reviewed by Rolleston and Jones was 24. I have examined 11 specimens from patients ranging from 14 to 63 years old, with a mean age of 34 years. The sexes are nearly equally affected but in some series there has been a predominance of females; my specimens were from 4 males and 7 females.

Malignancy and metastases

Although the appendical argentaffin carcinomas are less dangerous than the enteric ones, there is no justification for the term ‘carcinoid’. The growth often infiltrates the wall of the organ and reaches its peritoneal surface (Fig. 192) and there are many recorded cases with metastases in peritoneum, lymph glands, liver and elsewhere (see references by Stewart and Taylor, and Willis 1934).

METASTASIS OF CARCINOMA

(1) Metastasis by lymphatic channels

Careful dissection and microscopical study reveal regional lymph nodal metastases in the majority of cases, e.g. in 62 of 100 operation specimens of rectal cancer described by Gabriel *et al* in 505 of 1,000 operation specimens reported by Dukes and in 28 of 46 cases of colonic cancer described by Collier *et al*. The first glands to receive metastases are usually but not always those nearest the primary growth, metastasis then takes place to more remote glands. Glands which appear to the naked eye to be unaffected may be found microscopically to contain metastases but more often enlarged glands thought to be cancerous are found to show inflammatory changes only. As with carcinoma of other organs the presence or absence of lymph nodal metastases is a major factor in prognosis. Gabriel *et al* recorded the following percentages of 5 year survivals following excision of cancer of the rectum: when the tumours showed no extensions to the perirectal tissues 91 per cent; when the tumours had spread directly to the perirectal tissues but were unaccompanied by glandular metastases, 64 per cent; when glandular metastases were present, 16 per cent. For further details regarding lymphatic metastasis and prognosis see Dukes (1944).

Advanced intestinal carcinoma often shows tumour deposits in many groups of abdominal lymph glands and it is one of the three commonest tumours to invade the thoracic duct being surpassed in this respect only by gastric and uterine carcinoma.

(2) Transperitoneal metastasis

Peritoneal dissemination is present in about 20 per cent of fatal cases of cancer of the large bowel. Anson saw a case of carcinoma of the caecum, large pelvic deposits of which simulated primary rectal cancer.

Ovarian metastases occur in about 5 per cent of fatal cases and they have often simulated primary ovarian disease (Willis 1934). They are usually of adenocarcinomatous type and may be papillary, cystic or mucoid; they are rarely of Krukenberg type.

(3) Metastasis by the blood stream

(a) The liver

The liver contains secondary growths in one third or one half of fatal cases, e.g. in 31 of my 59 necropsies and in 57 of 170 in Brown and Warren's series. Of my 31 cases with hepatic deposits 11 had no other metastases. Goligher found that of 31 cases who had died a few days after excision of the rectum and whose livers had been thought clear of metastases at operation 5 cases were found at necropsy to have deposits deep in the liver. Very small primary growths in the bowel may produce gigantic enlargement of the liver: the biggest recorded liver weight is 33.3 pounds (15,110 grammes) from a case of carcinoma of the rectum (Christian). I have examined a liver weighing 11,000 grammes from a case of small annular carcinoma of the sigmoid colon and Kettle depicted a colonic growth $\frac{1}{4}$ inch in diameter which had produced a liver weighing

(2) Adenocarcinoma

Rectal adenocarcinoma of the ordinary kind may of course extend to the anal canal and perineum. In the following case, however, an adenocarcinoma of peculiar type arose in the anal canal, probably from the intramuscular glands which are present there.

Case V—History.—A man of 60 was admitted to hospital with symptoms of intestinal obstruction. He had had anal soreness for a year and more recent discharge and swelling. Rectal examination disclosed ill defined induration around the anal canal. *Necropsy* showed two thirds of the circumference of the upper part of the anal canal to be diffusely infiltrated by white growth which extended to the surrounding tissue. There were no metastases. The sigmoid colon contained a single pedunculated polypus 3 centimetres in diameter. *Histology* (Fig. 193).—The mucous membrane of the anal canal is intact



FIG. 193.—*Case V.* Adenocarcinoma of anal canal probably arising from the intramuscular glands ($\times 60$)

The sphincter muscle is infiltrated by a carcinoma composed of broad epithelial columns, in part solid and in part containing acinar spaces surrounded by multiple layers of cells. The sigmoid polypus is a benign adenoma of the usual type.

REFERENCES

- Anson, C. E. H. (1927) *Lancet*, 1 704.
 Ashworth, C. F. and Wallace, S. A. (1941) *Arch. Path.* 32 272.
 Brown, C. E. and Warren, S. (1938) *Surg. Gyn. Obst.* 66 611.
 Brust, J. C. M. and Bagen, J. A. (1934) *New Engl. J. Med.*, 210 692.
 Christian, H. A. (1903) *Amer. Med.* 5 131.
 Collier, F. A., Kay, E. B. and MacIntyre, R. S. (1941) *Ann. Surg.* 114 56.
 Dolbey, R. V. and Moore, A. W. (1924) *Lancet* 1 587.
 DUKES, C. E. (1926) Simple tumours of the large intestine and their relation to cancer.
Brit. J. Surg. 13 720.
 DUKES, C. F. (1930) The hereditary factor in polyposis intestinalis or multiple adenomata.
Cancer Rev. 5 241.
 DUKES, C. E. (1939) Ossification in rectal cancer. *Proc. Roy. Soc. Med.* 32 1489.
 DUKES, C. E. (1940) Cancer of the rectum: an analysis of 1,000 cases. *J. Path. Bact.* 50 527.

In most cases, however, removal of the appendix along with neighbouring lymph glands if these are affected is curative

(2) Adenocarcinoma of colonic type

This is a rare tumour in the appendix Rolleston and Jones reviewed 6 reported cases, Uihlein and McDonald described 5 cases Phillips and Isaac one case, and I have seen 2 examples The tumours share the age incidence,



FIG 192 —Infiltration of muscular coat by argentaffin carcinoma of appendix ($\times 120$)

structure and behaviour of their colonic counterparts Mucus secretion is often conspicuous It should be noted here that caecal carcinoma may invade the appendix or may cause obstructive appendicitis (Parker and Rosenthal Gordon Taylor

CARCINOMA OF THE ANUS AND ANAL CANAL

(1) Epidermoid carcinoma

Gabriel has given a good account of 55 cases of this disease, which in its structure and behaviour generally resembles the epidermoid carcinomas of the skin The mean age of Gabriel's cases was 62 and there were 27 men and 28 women There was however a decided difference between the sexes as regards the initial sites of the tumours those starting in the anal canal affected 23 women and 3 men while those of the anal margins affected 24 men and 5 women Metastasis occurs mainly to the inguinal lymph glands but the intrapelvic glands also may be affected

CHAPTER 24

CARCINOMA OF THE LIVER

USEFUL early reviews of the pathology of primary carcinoma of the liver include those of Weigert (1876), van Heukelom (1894) Eggel (1901), Wegelin (1905), Goldzieher and Bokay (1911) and Winternitz (1912), and more recent accounts, those of Counsellor and McIndoe (1926), Fox and Bartels (1928), Strong and Pitts (1930), and Stewart (1931). In this chapter, benign epithelial tumours of the liver are considered in their relation to carcinoma. Embryonic carcinoma of the infant's liver is described in Chapter 60.

I have studied the following 15 necropsy cases of hepatic carcinoma

Case No	Sex age	Description	Histology	Metastases
I	M 62	Main growth 9 centimetres no cirrhosis	Liver-cell carcinoma	Lymph glands liver peritoneum lungs kidneys adrenals pancreas gastric and intestinal mucosa gall bladder thyroid brain many bones
II	F 61	Single growth in cirrhotic liver	Liver-cell carcinoma	None
III	F 67	Single tumour replacing I lobe no cirrhosis	Liver-cell carcinoma	Peritoneum
IV	M 60 (Chinese)	Main growth 15 centimetres in cirrhotic liver	Liver cell carcinoma (+adenocarcinoma)	Liver
V	M 71	Multiple with haemochromatosis	Liver-cell carcinoma	None
VI	M 61	Multiple with haemochromatosis	Liver-cell carcinoma	None
VII	M 61	Multiple with haemochromatosis	Liver-cell carcinoma	None (portal vein invaded)
VIII	F 41	Large tumour no cirrhosis	Adenocarcinoma	Lymph glands liver peritoneum ovary bone (with paraplegia)
IX	M 64	Huge tumour in spirit drinker without cirrhosis	Adenocarcinoma	Liver (with multiple invasion of portal and hepatic veins) Tumour emboli in lungs

- DUKES, C E (1944) The surgical pathology of rectal cancer *Proc Roy Soc Med* 37 131
- DUKES C E (1945) *Ibid* 38 381
(Dukes's papers contain a wealth of accurate information derived from meticulous study of a large series of specimens)
- GABRIEL W B (1940) Squamous cell carcinoma of the anus and anal canal An analysis of 55 cases *Proc Roy Soc Med* 34 139
- GABRIEL W B, DUKES, C, and BUSSEY H J R (1935) Lymphatic spread in cancer of the rectum *Brit J Surg* 23 395
- Goligher J C (1941) *Brit Med J* ii 393
- Gordon Taylor G (1936) *Proc Roy Soc Med* 29 343
- Hayden E P and Shedden W M (1930) *Surg Gyn Obst* 51 783
- Kettle E H (1925) *The Pathology of Tumours* London
- LOCKHART MUMMIFRY J P and DUKES, C E (1939) Familial adenomatosis of colon and rectum its relation to cancer *Lancet* ii 586
- Norbury L E C (1930) *Proc Roy Soc Med* 24 198
- Ogilvie R F (1936) *Brit J Surg* 23 601
- Parker G E and Rosenthal D B (1933) *Lancet* ii 1089
- Phillips E W and Isaac D H (1930) *Brit Med J* i 1127
- Potter E B and Docter J M (1944) *Amer J Path* 20 143
- Raiford T S (1935) *Ann Surg* 101 863 1042
- ROLLESTON H D and JONES L (1906) Primary malignant disease of the vermiform appendix *Med Chir Trans* 89 125 (A useful review of earlier reports)
- Schlotthauer C F (1940) *N Amer Vet* 21 423
- Stewart M J and Taylor A L (1926) *J Path Bact* 29 136
- Stewart M J (1931) *Reference* Chapter 21
- Stout A P (1942) *Amer J Path* 18 993
- Swinton N W and Warren S (1939) *J Amer Med Assoc* 113 1927
- Uihlein A and McDonold J R (1943) *Surg Gyn Obst* 76 711
- Webster R (1938) *Med J Austral* ii 907
- Wells H G *et al* (1938) *Reference* Chapter 21
- Willis R A (1935) *J Path Bact* 40 187
- Willis R A (1934 and 1941) *References* Chapter 21

necropsy cases 58. Highly susceptible coloured peoples suffer at earlier ages, Berman found that 83 per cent of Bantu patients were 40 years old or less, 44 per cent being in the third decade.



Figs 194 and 195 —Liver-cell tumours of dogs ($\times 120$)

(3) Sex

The disease is commoner in men than in women, the ratio ranging between 2:1 and 12:1 in various recorded series. My 15 necropsy cases comprised 10 men and 5 women. In the Bantu, Javanese, Chinese and Japanese also there is a marked predominance of males.

Case No	Sex age	Description	Histology	Metastases
X	F 53	Huge growth no cirrhosis	Adenocarcinoma	Hepatic veins invaded Metastases in lymph glands and lungs
XI	M 70	Large tumour no cirrhosis	Adenocarcinoma	Liver lymph glands peritoneum bones kidney
XII	M 73	Main growth 20 centimetres no cirrhosis	Adenocarcinoma	Liver (with many veins invaded) lymph glands thoracic duct lungs adrenals
XIII	F 27	Carcinomatous change in congenital cysts	Adenocarcinoma	Liver lymph glands lungs
XIV	M 47	Huge tumour no cirrhosis	Anaplastic carcinoma	Lymph glands thoracic duct liver lungs kidneys dura mater peritoneum (including hernial sac)
XV	M 56	Main growth 20 centimetres no cirrhosis	Anaplastic carcinoma	Liver, lymph gland

Most of the cases have been reported elsewhere Nos V to VII in a paper on haemochromatosis in 1941 VIII to XI in a review of 500 necropsies in 1941 (Nos 341, 348, 349 and 421), No XIII in 1943 and No XIV in 1930

FREQUENCY RACE AGE, SEX AND SPECIES INCIDENCE

(1) Frequency and racial incidence

Primary carcinoma of the liver is a diagnosis which can be established only by thorough necropsy, mortality statistics of this disease are therefore valueless. It is rare in white skinned peoples in whom it is found in 0.1 to 0.3 per cent of all necropsies (Stewart) or in about 1 per cent of necropsies on cases of malignant disease. My 15 cases occurred in a consecutive series of 1,400 cancer necropsies. In this series there were 505 cases (36 per cent) with secondary growths in the liver, thus secondary growths were 34 times as frequent as primary growths.

Hepatic cancer is much commoner in some of the coloured races especially the Bantu, Javanese, Chinese and Japanese (Stewart, Bonne, Berman, Shear). Indeed it was the commonest malignant tumour in Bonne's Javan necropsies and in Berman's Bantu cases. Of great interest is Berman's observation that there are marked differences in incidence in different tribes of the same race, e.g. the East Coast Bantu appear to be six times more liable than the South African Bantu. The high incidence of hepatic cancer in African Negroes does not appear in Negroes in America (Kennaway 1944) it is therefore not a racial character, but is due to environmental factors.

(2) Age

In Europeans carcinoma of the liver is commonest in the sixth decade. The mean age in Counsellor and McIndoe's compiled series was 61.5, and of my 15

MODE OF ORIGIN

While solitary carcinomas of the liver often appear to be of unifocal origin multifocal origin is equally clear in other cases, e.g. in my haemochromatosis cases, in the case of carcinoma arising in a developmental cyst (No. XIII), and in Sanes and MacCallum's cases. When a tumour has invaded portal branch veins in the liver, however, it becomes difficult to decide whether multiple growths present have resulted from multifocal origin or intra-hepatic metastasis. Stewart was inclined to interpret all multiple growths as due to spread and metastasis within portal veins. While fully endorsing the importance and frequency of such spread, I believe that genuine multifocal origin obtains in many cases.

STRUCTURE

Two main types of structure are seen in carcinomas of the liver, (a) liver cell carcinoma or malignant hepatoma, and (b) adenocarcinoma of bile duct type or cholangioma. While many tumours fall into one or the other of these two classes, tumours of mixed structure also occur. I have seen several liver cell tumours which contained small areas of distinct columnar celled adenocarcinoma notably Case IV. Thus, while the distinction between hepatoma and cholangioma is useful, it is not a sharp one.

(a) *Liver cell carcinoma* (Figs 194-197) shows varying degrees of differentiation from a structure almost like normal liver tissue but without a proper lobular pattern to anaplastic growths with great cellular pleomorphism and much degeneration and haemorrhage. The better differentiated growths often secrete bile and stain themselves yellow or green, even in their metastases (references, Willis, 1934). Anaplastic tumours with multinucleated giant tumour cells and much haemorrhage may mimic the structure of chorion carcinoma (Cruckshank, L. Esperance).

(b) *Cholangioma* does not differ in structure or behaviour from the adenocarcinomas of the extra-hepatic bile ducts (q.v.).

METASTASIS

(1) Intra-hepatic portal metastasis

This occurs frequently. Portal branch veins, sometimes the main ones near the porta, often show invasion of their lumina and extension of the growths along them (Fig. 197), and metastatic growths are often present in the neighbourhood of the main growth or in distant parts of the liver. Stewart found portal veins invaded in 28 of 33 collected cases of liver-cell carcinoma, and in 5 of 11 cases of cholangioma. And I have referred to many records of invasion of portal or hepatic veins (Willis 1934). *Invasion of hepatic veins* is the prelude to metastasis to the lungs. Tumours invading the inferior vena cava have sometimes extended up this vessel into the right atrium (Counsellor and McIndoe, Loehlein).

(2) Pulmonary metastases

These are recorded in about one fifth of fatal cases and were present in 5 of my 15 cases. As with other abdominal carcinomas the lungs may contain many intravascular tumour emboli without visible metastases (e.g. my Case IX).

(4) Hepatic carcinoma in animals

This disease is not unusual in cattle and sheep (Feldman 1932) and in dogs, less common in cats horses pigs and other species (Feldman 1936, Winer and Schroeder 1940) Norris saw an adenocarcinoma of the liver in a rooster Rudduck and I studied the following liver tumours in animals

- Dogs*
- (1) Fox terrier, male aged 13 Multiple liver cell tumours largest 6 centimetres in cirrhotic liver (Fig 194)
 - (2) Airedale male, aged 14 Multiple small liver cell tumours in cirrhotic liver
 - (3) Fox-terrier male aged 13 Solitary liver cell tumour 10 centimetres in diameter (Fig 195)

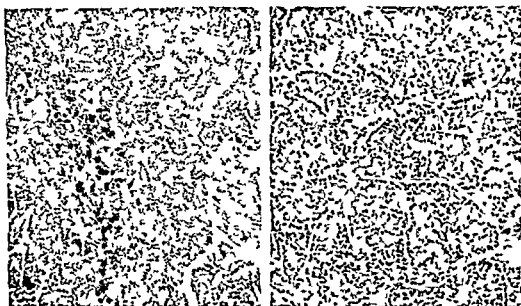


FIG 196—Liver-cell tumour of frog note alveolar structure and included pigment-cells ($\times 60$ and 120)

- (4) Collie female aged 12 Liver-cell tumour 15 centimetres in diameter
- (5) Mongrel male aged 15 Liver cell tumour 10 centimetres in diameter
- (6) Foxhound male aged 7 Papillary adenocarcinoma 15 centimetres in diameter with many metastases in liver, peritoneum and lymph glands

Persian cat aged 15 Adenocarcinoma 10 centimetres in diameter

Frog (*Rana esculenta*) adult Solitary tumour white but with black mottling from included pigment cells of liver 3 centimetres in diameter, microscopically a well differentiated hepatoma (Fig 196)

CAUSATIVE FACTORS**(1) Cirrhosis**

As a pre-cancerous lesion cirrhosis has been discussed by many of the writers

CHAPTER 25

EPITHELIAL TUMOURS OF THE BILIARY TRACT

IN THIS chapter we will consider

- (a) Benign epithelial tumours
- (b) Carcinoma of the gall bladder
- (c) Carcinoma of the extra-hepatic bile ducts

BENIGN EPITHELIAL TUMOURS OF THE BILIARY TRACT

Polypoid and cystic cholecystitis (cholecystitis glandularis proliferans) has often been misnamed "papilloma" or "adenoma", as in a paper by Shepard *et al* (1942). True papillomas and adenomas of the bile channels are rare. In 1936 Kerr and Lendrum could find records of only 7 fully acceptable cases of papilloma of the gall bladder to which Brown and Cappell (1937) added an eighth. The papilloma of the gall-bladder described by Kerr and Lendrum was remarkable in that it consisted of intestinal epithelium, including Paneth cells, goblet cells and argentaffin cells, and that it secreted large quantities of salt and water. Multiple papillomas of the gall bladder, like that described by Brown and Cappell, were attributed by Kerr and Lendrum to transplantation, but a preferable interpretation is that they are, like the multiple papillomas of the intestine or stomach of multicentric origin. I have examined a pedunculated papilloma 1 centimetre in diameter in the gall bladder of a sheep.

CARCINOMA OF THE GALL BLADDER

(1) Incidence, site, etc

(a) Frequency

English and American surgical and necropsy records show that carcinoma of the gall bladder occurs with about one tenth the frequency of carcinoma of the stomach and constitutes about 3 per cent of fatal cases of carcinoma (Illingworth Mohardt, Kirshbaum and Kozoll). In my 1,060 necropsy cases of carcinoma (Table V, Chapter 5) there were 26 of carcinoma of the gall bladder.

(b) Age

The mean age in various series ranges from 57 to 63. More than half the patients are in the sixth and seventh decades. The disease is very rare under 40. The youngest of my 26 necropsy cases was 44 years of age.

(c) Sex

Women are affected more frequently than men, in a ratio of about 3 or 4 to 1 (references by Mohardt). My necropsies comprised 18 women and 8 men.

(d) Site and extent of origin

Many of the tumours are so extensive when first seen that their precise sites of origin cannot be specified, but the neck and fundus appear to be more often

(3) Other metastases

Other blood borne metastases chiefly in the bones are less frequent. Skeletal or other metastases may clinically simulate primary disease or may be the first signs of illness as in my Case VIII with paraplegia and Moon's case with pathological fracture of the femur.

Lymph nodal peritoneal or ovarian metastases occur in perhaps one quarter of fatal cases.

REFERENCES

- BERMAN C (1941) The etiology of primary carcinoma of the liver—with special reference to the Bantu races of South Africa. *S African J Med Sci* 6 145
- Bonne C (1935) *Amer J Cancer* 25 811
- Counsellor V S and McIndoe A H (1926) *Arch Int Med* 37 363
- Cruickshank J (1910) *J Path Bact* 14 282
- Eggel H (1901) *Beitr path Anat* 30 506
- L Esperance E S (1915) *J Med Res* 27 225
- Feldman W H (1932) *Neoplasms of Domesticated Animals* pp 299 311 Philadelphia
- Feldman W H (1936) *Amer J Cancer* 27 111
- Fox R A and Bartels G W (1928) *Arch Path* 6 228
- GOLDZIEHR, M and BOKAY, Z (1911) Der primäre Leberkrebs. *Virchows Arch* 203 75
- van Heukelom S (1894) *Beitr path Anat* 16 341
- Hueper W C (1942) *Occupational Tumors* pp 342 et seq Springfield
- Kennaway E L (1944) *Cancer Res* 4 571
- Loehlein W (1907) *Beitr path Anat* 42 531
- Norris J C (1936) *Amer J Cancer* 26 778
- Sanes S and MacCallum J D (1942) *Amer J Path* 18 675
- Shear M J (1937) *Amer J Cancer* 29 269
- STEWART M J (1931) Precancerous lesions of the alimentary tract. *Lancet* ii 565 (Discusses the relation of hepatic cancer to cirrhosis, haemochromatosis and parasitic disease)
- Strong G F and Pitts H H (1930) *Arch Int Med* 46 105
- WECELIN K (1905) Über das Adenokarzinom und Adenom der Leber. *Virchows Arch* 179 95
- Weigert C (1876) *Virchows Arch* 67 500
- Willis R A (1930) *Med J Austral* ii 606
- Willis R A (1934) *The Spread of Tumours in the Human Body* pp 13 and 106 London
- Willis R A (1941) *Med J Austral* ii 258
- WILLIS, R A (1941) Haemochromatosis with special reference to supervening carcinoma of the liver. *Med J Austral* ii 666
- Willis R A (1943) *J Path Bact* 55 492
- Winer J H and Schroeder C R (1940) *Amer J Cancer* 38 268
- WINTERNITZ M C (1912) Primäres Leberkarzinom. *Virchows Arch* 209 239

amounts, and further investigations of large pooled quantities of gall-stones or the liquid contents of cancerous gall bladders should be undertaken

(b) *Cholecystitis*

This is present in many cancerous gall bladders but it is doubtful if it itself is a significant causative factor. It may be only a concomitant of the associated gall stones, or may result from obstructive effects of the growth itself. However, it must be admitted with Stewart, that a possible sequence of events in many cases may be cholecystitis, cholelithiasis, carcinoma.

It has often been suggested that carcinoma may supervene on polypoid and cystic cholecystitis but this sequence, which by analogy with transformations well known in other regions is quite a probable one, has not and cannot be readily demonstrated. It would be well nigh impossible to distinguish microscopically between an area of proliferative cholecystitis with supervening carcinoma and an area of well differentiated adenocarcinoma. Proliferative cholecystitis with its invasion of the entire thickness of the gall bladder wall by the glands has itself often been mistaken for carcinoma e.g. by several of the experimentalists reviewed by Burrows. There is no evidence that the strawberry gall bladder is predisposed to cancer.

(3) Structure

The gross form of the tumours varies. The most frequent is the infiltrating scirrhus type leading to diffuse thickening of part or the whole of the wall and spreading to surrounding tissues. Less common are polypoid and papillary growths projecting into and distending the lumen. Combinations of the two types of growth are seen, and sometimes gelatinous change is prominent.

Microscopically, most of the tumours are infiltrating adenocarcinomas of varying degrees of differentiation. Mucus secreting adenocarcinoma is quite common but diffusely infiltrating signet ring cell carcinoma is rare. Undifferentiated carcinomas also are infrequent. Squamous metaplasia is present in some degree in about 10 per cent of the tumours and is sometimes prominent throughout. In my experience however, it is never complete but is always associated with adenocarcinomatous structure. There is no evidence to support the statement sometimes made that the growths showing epidermoid metaplasia have arisen in areas of mucosa in which metaplasia had previously been present. The change takes place in the growths themselves, squamoid change is not seen in non-neoplastic lesions of the gall bladder.

(4) Metastasis

Lymph glands contain deposits of growth in a high proportion of fatal cases e.g. in 18 of my 26 necropsies, and in 34 of 55 in Kirshbaum and Kozoll's series, the glands along the cystic duct and in the porta of the liver are the earliest affected. Cappell and Tudhope described a case in which a small unsuspected carcinoma of the gall bladder had produced widespread metastases in lymph glands and had led to a diagnosis of 'lymphadenoma or lymphosarcoma'. The liver contains discrete metastases in more than one half of the cases e.g. in 16 of my 26 necropsies.

affected than intermediate parts. Multiple separate areas of growth are not unusual, I have seen several unequivocal examples, and there is no doubt that more thorough examination of gall bladders with early carcinomas would often show these to be of multicentric or widespread and progressive origin. A frequent form of cancerous gall bladder with extensive uniform thickening of the wall, resembling the leather bottle stomach may well be attributed as much to extensive origin as to extensive spread of the growth, and this interpretation is strengthened by frequent instances of widespread carcinomatous disease affecting the walls of the gall bladder and main bile ducts simultaneously (Wilks 1942).

(e) *Race and species*

Carcinoma of the gall bladder occurs quite commonly in American negroes (Kirschbaum and Kozoll). It is recorded infrequently in some Oriental races e.g. in Java, where gall stones also are uncommon (Bonne). In animals cancer of the gall bladder has been seen occasionally in the ox, dog and fowl (Feldman).

2) Causative factors

(a) *Gall stones*

These have been present in from 60 to 100 per cent of cases in different series (Stewart Mohardt), they were present, or had been present in 24 of my 26 necropsy cases. There is no doubt that the stones precede the growths in most cases and it is of interest that cancer may develop many years after removal of stones. 24 years in one of my cases (1942). The stones most commonly present in the cancerous gall bladder are of the multiple pigmented type. Solitary pure cholesterol stones are also encountered but Stewart found that these did not occur with greater frequency in cancerous cases than in control cases.

The frequent association of stones with cancer of the gall bladder has led to many attempts to produce this disease experimentally in animals by inserting gall stones and other foreign bodies into the organ. These have included pebbles, suture materials, lanoline paraffin pitch tar cement pumice and tile fragments. The experiments were fully reviewed by Burrows (1933) who also carried out personal experiments with gall stones, plaster of Paris pellets containing cholesterol pellets containing dibenzanthracene and pieces of sponge soaked in fat containing dibenzanthracene (1933 and 1939). Burrows obtained inflammatory proliferations resembling human polypoid cholecystitis but no tumours and from his review it was clear that this had been the case also with the results of earlier workers, some of whom had claimed to have produced tumours. Nearly all the experiments of this kind have been on the guinea pig, an animal which seldom develops spontaneous tumours and which is also refractory to the experimental production of skin tumours. Further attempts to produce cancer of the gall bladder should be made on other species.

Hypothetically stones from cancerous gall bladders might well contain chemical carcinogens. Professor E. L. Kennaway and Dr I. Hieger kindly examined several such stones which I sent them but found nothing distinctive spectrographically in extracts which also failed to produce skin tumours in mice. However naturally occurring carcinogens might be present in very minute

Kirshbaum and Kozoll's cases In my 1942 series, none of the 15 cases of bile duct cancer had stones in the affected ducts, but in 3 cases the gall bladder contained stones, and in all 3 cases of combined carcinoma of the ducts and gall bladder stones were present in the gall bladder *Cholecystitis and cholangitis* are of doubtful causative importance in duct cancers

(3) Structure

Whether taking the form of diffuse thickening of long reaches of the ducts or annular stenoses or bulkier nodular growths, most of the tumours are infiltrating scirrhous adenocarcinomas, occasionally with mucoid areas Projecting papillary carcinoma is infrequent I have not seen squamous metaplasia in any of my specimens, nor have I seen it described

(4) Metastasis

Metastases are less frequent than with carcinomas of the gall bladder, probably because early biliary obstruction proves fatal before the tumours have extended far Lymph glands were affected in 28 of Kirshbaum and Kozoll's 62 necropsies In my 15 cases (1942) metastases were present in lymph glands in 3 cases, in the liver in 3, in the peritoneum in 4, and in the lungs in 2 cases

REFERENCES

- Bonne C (1935) *Amer J Cancer* 25 811
 Brown F R and Cappell D F (1937) *Brit J Surg* 24 703
 BURROWS, H (1933) An experimental enquiry into the association between gall stones and primary cancer of the gall bladder *Brit J Surg* 20 607
 Burrows H (1939) *Brit J Surg* 27 166
 Cappell D F and Tudhope G R (1934) *Glasgow Med J* 122 185
 Feldman W H (1932) *Neoplasms of Domesticated Animals* pp 300 309 314 Philadelphia
 Foggie W E and Tudhope G R (1930) *Edinb Med J* 37 632
 Illingworth C F W (1935) *Brit J Surg* 23 4
 KERR, A B, and LENDRUM, A C (1936) A chloride secreting papilloma in the gall bladder *Brit J Surg*, 23 615 (An admirable histological study of a remarkable specimen)
 KIRSHBAUM, J, D and KOZOLL, D D (1941) 'Carcinoma of the gall bladder and extra hepatic bile ducts', *Surg Gyn Obst*, 73 740 (A useful general account of 117 necropsy cases)
 Mohardt J H (1939) *Internat Abst Surg*, 69 440
 Shepard V D, Walters W and Dockerty M B (1942) *Arch Surg*, 45 1
 Stewart M J (1931) *Lancet* ii 617
 WILLIS, R A (1942) Some aspects of the pathology of carcinomata of the biliary tract, *Med J Austral* ii 340

Other sites of metastasis include the lungs bones and ovaries, Foggie and Tudhope described a patient in whom the clinical and radiographic findings were those of primary cancer of the lung but necropsy disclosed this to be a metastasis from a carcinoma of the gall bladder

CARCINOMA OF THE EXTRA HEPATIC BILE DUCTS

(1) Incidence, site, etc

(a) Frequency

Contrary to the general impression of clinicians carcinoma of the main bile ducts is at least as frequent as carcinoma of the gall bladder on the one hand and carcinoma of the pancreas on the other. The belief that the pancreas is a much commoner site of cancer than the bile ducts is due to misdiagnosis of many cases of cancer of the common duct as cancer of the head of the pancreas. Adequate necropsy study of the distribution of tumours in this region soon exposes this error. In a 5 year period during which I directed special attention to the sites of carcinomas of the bile passages and of the pancreas seen at necropsy I encountered 11 carcinomas of the gall bladder 3 of the gall bladder and bile ducts 15 of the bile ducts and 14 of the pancreas (1942). In Kirshbaum and Kozoll's necropsy series there were 55 carcinomas of the gall bladder 62 of the extra hepatic bile ducts and 41 of the head of the pancreas. Like myself (Chapter 5 Table I) these workers found a high proportion of clinical misdiagnoses in this region in both their series and mine carcinoma of the gall bladder and bile ducts had been correctly diagnosed in only 22 per cent of cases.

(b) Age

The age distribution is about the same as for cancer of the gall bladder more than half of the patients are in the sixth and seventh decades and patients under 40 years are rare.

(c) Sex

Unlike cancer of the gall bladder, that of the ducts is slightly more frequent in men than in women e.g. 17 men and 15 women in my necropsies and in the ratio of 55 and 45 per cent in Kirshbaum and Kozoll's series.

(d) Site

Kirshbaum and Kozoll recorded 7 carcinomas of the cystic duct 13 of the hepatic ducts 32 of the common duct and 10 of the papilla. In my 1942 study 10 of 15 duct cancers affected the common duct only 3 the hepatic ducts only one the common and cystic ducts and one the hepatic cystic and common ducts. In addition as mentioned above there were 3 cases in which extensive cancer of all the main ducts coexisted with cancer of the gall bladder. Stenosing growths restricted to short segments of the bile ducts are most frequent in or just above the ampulla of Vater and it is these growths that are often confused with carcinomas of the head of the pancreas.

(2) Causative factors

Gall stones are present in only a minority of cases e.g. in 31 per cent of

observed widespread pancreatic changes which were structurally adenocarcinomatous but without metastases

(2) Causative factors and mode of origin

Nothing is known of the causation of pancreatic carcinoma. Inflammatory changes in the pancreas accompanying cancer are in most cases clearly secondary to duct obstruction caused by the growths. Neither pancreatic nor biliary stones are found with disproportionate frequency. Haemochromatosis does not predispose to carcinoma of the pancreas. There is no evidence that heterotopic pancreas, in the stomach, intestine or Meckel's diverticulum, is specially prone to tumour formation, though instances of carcinoma of heterotopic pancreas have occurred (*see* Nicholson's case referred to in Chapter 21)



FIG 201—Acinar type of adenocarcinoma. The growth was an early one 4 millimetres in diameter, found in the tail of the pancreas at necropsy on a woman aged 73 ($\times 120$)

Korpassy observed metaplasia with stratification of the epithelium of the pancreatic ducts, mainly in elderly people but there is no reason to suppose this to be pre cancerous, as squamous metaplasia is rare in pancreatic carcinoma. Haban described the multicentric or diffuse origin of papillary carcinoma in the ducts.

(3) Structure and growth

In the great majority of cases cancers of the pancreas are adenocarcinomas of varying degrees of anaplasia, undifferentiated tumours of spheroidal celled or diffusely cellular anaplastic types are uncommon. Most of the adenocarcinomas are columnar celled and probably derived from the ducts. Others display a small acinar type of structure reminiscent of the secreting tissue of the pancreas (Fig 201). Sharp separation of ductal and acinar growths, however, is not

CHAPTER 26

EPITHELIAL TUMOURS OF THE PANCREAS

EPITHELIAL tumours of the pancreas comprise

- (a) Benign cystadenomas
- (b) Carcinomas of ducts and acini
- (c) Adenomas and carcinomas of islets of Langerhans

BLNIGN CYSTADENOMAS

These are well circumscribed rounded tumours sometimes small and discovered only incidentally at necropsy or operation, sometimes large enough to cause symptoms. The smaller tumours consist of a honeycomb of spaces, lined by columnar or cuboidal epithelium similar to that of the pancreatic ducts and containing mucinous secretion (Fig 198). Large tumours also are often multi-locular but in some cases one cyst attains a great size and the others are compressed in its walls. Papillary growth of the epithelium is frequent. Examples of large benign cystadenomas have been described by Carling and Hicks, Janes, and Bowers *et al*, and of their malignant counterparts by Kennard (*see also Case I below*). Cystic tumours must be distinguished from polycystic disease of the pancreas, a widespread change of developmental origin (Nygaard and Walters).

CARCINOMAS OF DUCTS AND ACINI

(1) Frequency, age, sex, site and species incidence

(a) *Frequency*

The proportion of clinical misdiagnoses in this disease is so high that the mortality figures are of little or no value (*see Chapter 5*). The only reliable sources of data for assessing the frequency and other properties of the disease are series of proved necropsy cases. There is little doubt that many cases called carcinoma of the head of the pancreas at operation or even at necropsy, are really cases of carcinoma of the lower part of the bile duct (*see Chapter 25*).

Recognition of this confusion of the two diseases would result in a diminished number of tumours recorded as pancreatic and an increased number recorded as biliary in origin. My necropsies included 42 proved cases of carcinoma of the pancreas compared with 227 of the stomach, 190 of the large intestine and 58 of the biliary tract.

(b) *Age*

The highest numbers of cases occur in the sixth and seventh decades. Of Wallaus's 330 necropsy cases, 54 per cent were between 50 and 70 years old and 73 per cent between 40 and 70. In Duff's series of 50 necropsy cases the corresponding percentages were 52 and 72. The mean ages in Wallaus's

by growth and distended with mucus and tumour deposits were present in lymph glands along the course of the thoracic duct and in the left supraclavicular fossa. Liver and other abdominal organs were free from growth. The lungs were enlarged and heavy, weighed 64 and 55 ounces and showed widespread gelatinous infiltration partly diffuse and ill defined and partly as well defined patches up to 6 centimetres in extent. All the bronchi were filled with tenacious mucus. The hilar lymph glands contained gelatinous growths. *Microscopy*—The pancreatic growth was a well differentiated columnar celled adenocarcinoma. The lungs were infiltrated throughout by mucoid adenocarcinoma consisting partly of columnar-celled growth which tended to line the invaded pulmonary



FIG 203—Case II Phagocytes accompanying the mucus produced by the tumour in the lung ($\times 200$)

air sacs (Fig 202) and partly of mucinous lakes containing isolated tumour cells. Accompanying the mucus in air sacs and bronchi were many phagocytic foam-cells and giant-cells (Fig 203). Monilia was present in the mucus. There was little or no true pneumonic change. *Diagnosis*—Symptomless carcinoma of pancreas invasion of thoracic duct massive mucoid metastases in lungs especially occupying air spaces growth of monilia in the mucus expectoration of mucus with monilia leading to false diagnosis of moniliasis.

The amount of destruction of pancreatic tissue effected by cancerous disease varies greatly. Often the tumours are relatively small, occasionally the whole pancreas is replaced by the growth. Even massive replacement of the pancreas does not necessarily produce diabetes for the islets of Langerhans may long remain intact in areas of tumour which has destroyed all the external secretory tissue. Sometimes however, extensive cancerous disease does produce diabetes, as in an interesting case which I have described elsewhere (1941). Marble has discussed the association of diabetes with malignant disease generally, including 33 cases of pancreatic carcinoma.

(4) Metastasis

Lymph glands contain tumour deposits in most fatal cases, e.g. in 30 of my

practicable. The possible occurrence of argentaffin carcinoma in the pancreas should be borne in mind (*see below*).

Most of the pancreatic adenocarcinomas are solid growths with no special characters. But a few tumours show prominent mucoid or cystic changes. Mucoid carcinomas have been reviewed and described by Hemken, and papillary cystadenocarcinomas by Kennard. The following case of cystic carcinoma is noteworthy.



FIG. 202.—Case II. Metastatic mucoid columnar-celled adenocarcinoma occupying pulmonary alveoli. ($\times 120$)

Case I—History—A woman 45 years old had first noticed a left upper abdominal mass 2 years previously. Exploration showed this to be a single large cyst of the tail of the pancreas with thickened walls adherent to surrounding parts. The contents was turbid brownish fluid with a high diastase content. **Necropsy** showed the tail of the pancreas replaced by a well-defined rounded cystic tumour 10 centimetres in diameter partly thin walled and partly thick walled with nodular masses of growth sprouting into the cavity. The head and neck of the pancreas contained several small ill-defined separate areas of solid white growth. Multiple metastatic tumours were present in neighbouring lymph glands liver lungs and kidneys. **Microscopy**—The cystic growth showed well differentiated papillary cystadenocarcinoma with some cellular anaplastic areas. All other tumours were of the latter kind.

The following interesting example of mucoid carcinoma is notable also because of a peculiar error in diagnosis.

Case II—History—For some months a man of 62 had suffered from cough with abundant mucoid sputum from which monilia was repeatedly cultured. There were signs and X-ray appearances of widespread patchy pneumonic change and the clinical diagnosis was pulmonary moniliasis. **Necropsy** showed an ill-defined carcinoma 3 centimetres in diameter in the body of the pancreas with deposits in surrounding lymph glands and some diffuse infiltration of the retroperitoneal tissues. The cisterna chyli was enveloped

EPITHELIAL TUMOURS OF THE PANCREAS ADENOMAS AND CARCINOMAS OF THE ISLETS

(1) Islet adenomas

Islet adenomas are not rare. They appear as small circumscribed nodules discovered incidentally at necropsy (Korpassy, and Fig 206), or are clinically

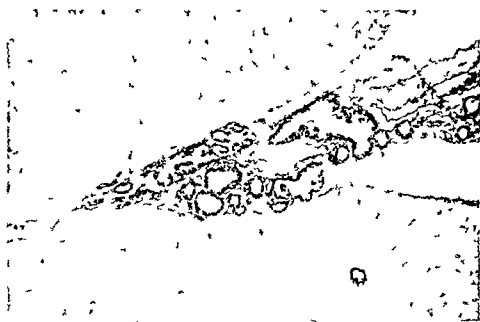


FIG 205—Case III. Microscopic infiltration of the meninges in a cerebral sulcus ($\times 35$)

FIG 206—A small islet adenoma found at necropsy on a woman aged 67 ($\times 120$)

important in producing hyperinsulinism (Whipple and Frantz, Frantz, Haines). Even when productive of symptoms, most of the tumours are less than 2 centimetres in diameter, but larger tumours, up to 500 grammes, have been seen

42 necropsies *Peritoneal dissemination* also occurs frequently, especially from cancers of the body and tail

The liver contains metastases in about two thirds of fatal cases e.g. in 192 of Wallau's 330 and in 29 of my 42 necropsies. The point of entry of the tumour into the portal circulation is often demonstrable in the splenic or portal veins or their main tributaries (Duff). Other sites of blood borne metastases are less frequent the commonest being the lungs which are affected in about one fifth of fatal cases. In a remarkable case reported by Hegler and Wohlwill there were splenic enlargement rarefying lesions in bones seen in skiagrams and

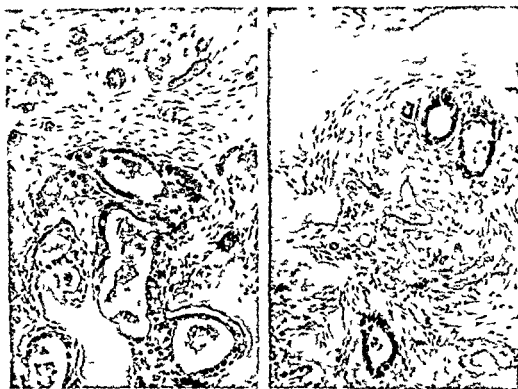


FIG 204—Case III Metastatic adenocarcinoma of vertebra ($\times 120$)

multiple subcutaneous lesions thought to be blastomycotic. necropsy disclosed an adenocarcinoma of the tail of the pancreas with metastases in bone marrow and subcutaneous tissues in which pronounced fat necrosis suggested that the tumour cells had continued to secrete digestive ferments. Metastases in the brain though infrequent may attain a large size and may simulate primary cerebral disease (Foot *et al* Dickson and Reynell Willis 1941). The following case showed unusual metastases

Case III—Male 64 Clinical diagnosis pulmonary fibrosis. *Necropsy*—Carcinoma of head of pancreas 4 centimetres in diameter not involving bile duct with deposits in neighbouring lymph glands and in peritoneum. Multiple metastases in liver lungs both adrenals thyroid and several vertebrae. Brain showed slight milky opacities of pia-arachnoid and felt slightly slimy but no definite metastases found. *Microscopy* (Figs 204 and 205)—Well-differentiated adenocarcinoma in all situations. diffuse microscopic infiltration of meninges by growth with slight extensions into brain.

- Wilder R M Allan F N, Power M H and Robertson H E (1927) *J Amer Med Assoc*,
89 348
- Willis R A (1936) *J Path Bact* 42 203
- Willis R A (1940 and 1941) *Med J Austral* 1940, ii 400 1941, ii, 258

Their most frequent site is the tail but they may be found in any part of the pancreas and multiple tumours occur. Although well defined to the naked eye adenomas are often not encapsulated but show marginal infiltration of the surrounding pancreatic tissue. Sharp microscopic distinction between benign and malignant islet cell tumours is not possible.

(2) Islet carcinoma

This was first described by Wilder *et al* (1927) whose patient had suffered from hypoglycaemic attacks and who demonstrated the presence of insulin in the hepatic metastases as well as in the primary tumour at necropsy. Duff referred to 6 subsequent reports of islet-cell carcinoma and recorded a case with wide spread metastases. Three of these cases had shown evidence of hyperinsulinism, proving their nature. Frantz, Flinn *et al*, Gray and others have reported additional cases of insulin secreting islet cell carcinomas with hepatic metastases. Caution is needed however in identifying 'islet cell carcinomas' from their structure alone when no clinical or chemical evidence of insulin secretion is demonstrable. In structure a disorderly islet cell tumour might closely resemble a disorderly argentaffin carcinoma, such as my case (No. 330) of diffuse carcinoma first described in 1936 and later (1940) identified as of argentaffin type. Frantz properly emphasized that islet adenomas and carcinomas are not sharply separable, islet tumours form a single group with a wide range of behaviour, slowly growing localized tumours predominating.

REFERENCES

- Bowers R F, Lord J W and McSwain B (1942) *Arch Surg* 45 111
 Carling E R and Hicks J A B (1926) *Brit J Surg* 13 238
 Dickson W E C and Reynell W (1929) *Proc Roy Soc Med* 23 530
 DUFF, G L (1939) The clinical and pathological features of carcinoma of the body and tail of the pancreas. *Johns Hopk. Hosp Bull* 65 69
 Flinn L B, Beatty G A, Ginsberg M and Hemsath F A (1941) *J Amer Med Assoc* 117 283
 Foot N C, Carter B N and Flipse M J (1924) *Amer J Med Sci* 167 76
 FRANTZ V K (1940) Tumors of islet cells with hyperinsulinism: benign, malignant and questionable. *Ann Surg* 112 161 (A valuable supplement to Whipple and Frantz's review)
 Gray L M (1942) *Amer J Path* 18 633
 Habán G (1936) *Virchows Arch*, 297 207
 Haines M (1946) *J Path Bact* 58 104
 Hegler C and Wohlwill F (1930) *Virchows Arch* 274 784
 Hemken L (1936) *Arch Path* 21 351
 James R M (1936) *Brit J Surg* 23 809
 KENYARD H E (1941) Papillary cystadenocarcinoma of the pancreas, *Surg* 9 65
 Kiefer E D (1927) *Arch Int Med* 40 1
 Korpássy B (1939) *Virchows Arch* 303 359
 Marble A (1934) *New Engl J Med* 211 339
 Mielcarek P A (1935) *Amer J Path* 11 527
 Nygaard K K and Walters W (1937) *Ann Surg* 106 49
 Ratchiffe H L (1943) *Amer J Path* 19 359
 Slye M, Holmes H F and Wells H G (1935) *Amer J Cancer* 23 81
 Wallau F (1932) *Virchows Arch* 283 321
 WHIPPLE, A O and FRANTZ, V K (1935) Adenoma of islet cells with hyperinsulinism. *Ann Surg* 101 1299 (An excellent review)

2 centimetres or more in diameter, but most of them are less than 1 centimetre. They are frequently multiple, and are often present in both kidneys. The kidneys almost always show distinct evidence of arteriosclerotic or chronic nephritic



FIG 208 —Adenoma of kidney, papillary type with granular calcification ($\times 120$)

changes. Adenomas are found chiefly in middle-aged or old people and are uncommon in youth. My specimens came from 26 men and 15 women, whose mean age was 52 years.



FIG 209 —Adenoma of kidney, collections of foam cells in the stroma ($\times 120$)

(2) Structure

Figs 207-210 depict some of the commoner appearances. Many of the tumours show a predominant intra-cystic papillary structure, justifying Newcomb's

CHAPTER 27

ADENOMA AND CARCINOMA OF THE KIDNEY PARENCHYMA

EPITHELIAL tumours of the kidney are of the following distinct types

- (a) Adenomas and carcinomas of the uriniferous tubules of the adult kidney, the subject of the present chapter
- (b) Papillomas and carcinomas of the transitional stratified epithelium of the renal pelvis to be described in the next chapter
- (c) Embryonic tumours or nephroblastomas of the foetal or infant kidney (see Chapter 60)

ADENOMA OF THE KIDNEY

(1) Frequency, number, distribution, etc

In necropsy work it is common to discover small nodules of various kinds in the kidneys. Most of these are adenomas: fibrous medullary nodules, small cysts with inspissated contents, small leiomyomas, nodules of adrenal cortex and small lipomas, in that order of frequency. With the exception of the rather common small fibrous nodules, usually 3 or 4 millimetres in diameter, found in the medulla of both young and old kidneys, nearly all of the foregoing are cortical in position. Microscopical examination is necessary to distinguish the several kinds of nodules from one another. Most of them prove to be cortical adenomas.

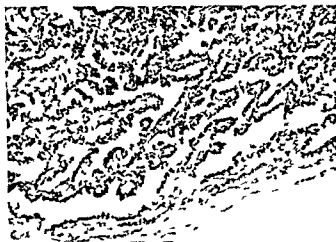


FIG 207 —Adenoma of kidney papillary type ($\times 120$)

These have been well described by Nicholson (1923), Newcomb and Trinkler, with whose findings my own are in substantial agreement.

Cortical adenomas of the kidney appear as well defined, but often not encapsulated, rounded or somewhat pyramidal nodules, usually yellow in colour and either solid or cystic. They vary in size from just visible dimensions up to

to say—just as in the breast, thyroid and liver it is often difficult to distinguish sharply between hyperplasia and neoplasia

Are adenomas related to carcinomas? Anyone who has examined and compared the structure of these tumours will have no hesitation in joining Newcomb and Trinkle in a strongly affirmative answer. Indeed, a sharp separation of adenomas and carcinomas is not possible. Some adenomas show a structure indistinguishable from that of carcinomas, and it is purely a matter of opinion whether we regard such tumours as atypical adenomas or as young carcinomas which we happen to have discovered before they have metastasized. Many an "adenoma" found incidentally at necropsy differs not one whit from some of those small symptomless carcinomas which have produced precocious metastases. Renal tumours, like other tumours, differ in their individual rates of growth, invasiveness and metastasizing proclivities. It is proper that those tumours which for long periods grow slowly, attain a uniform highly differentiated structure and fail to spread should be called 'adenomas' to distinguish them from their more active fellows and it is of course true that most of these more active growths show plain signs of their activity in their size, structure and invasiveness. But there are no structural criteria which will permit clear cut separation of the "black sheep" from the other members of the family.

CARCINOMA OF THE KIDNEY

Excluding the tumours of the renal pelvis and the embryonic nephroblastomas, all of the remaining malignant epithelial tumours of the kidney form a single group. Attempted sub division of this group of common renal tumours arises either from antiquated views on histogenesis or from ignorance of the wide range of structure to be seen in the group and even in one tumour. "Gravitz tumour", 'hypernephroma', 'clear celled carcinoma', 'solid-celled carcinoma', etc are not separate kinds of tumours, but merely names which have been given to the single entity *carcinoma of the renal parenchyma*. In what follows then, we deal with this entity without regard to artificial distinctions, the falsity of which will appear in the discussion. Of the many papers on the origin, structure and behaviour of renal carcinomas those of Sudeck, Manasse, Albrecht, Stoerk, Zehbe, Ipsen, Wright and Nicholson are of special value.

(I) Incidence and causation

(a) Incidence

The incidence of renal carcinoma is difficult to assess, because of the frequency with which clinical and pathological misdiagnoses have been made in this disease. Microscopically proven necropsy series are the only reliable source of data for estimating the true frequency and other properties. Of my 1060 carcinoma necropsies (Table V Chapter 5), renal carcinoma accounted for 27 cases, i.e. 2½ per cent. This was about one tenth of the frequency of gastric carcinoma and one third the frequency of pulmonary carcinoma.

(b) Age

The highest proportion of cases is seen in the sixth decade and about 50 per cent are in the fifth and sixth decades. The mean age at death of my 27 necropsy

designation 'papilliferous cyst adenoma' others show tubular or solid areas, and all kinds of structure may be seen in one nodule. In many tumours the epithelium consists mainly of small solid cubical cells but in other tumours the cells are larger, vacuolated or foamy, and closely resemble those of the clear celled renal carcinomas, and solid and clear cells may occur in one tumour. Common structural features attributable to secondary changes include accumulations of phagocytic foam cells in the stroma of the tumours, granular calcification, intra cystic haemorrhage, and deposition of blood pigments in the epithelial cells and in the stroma.

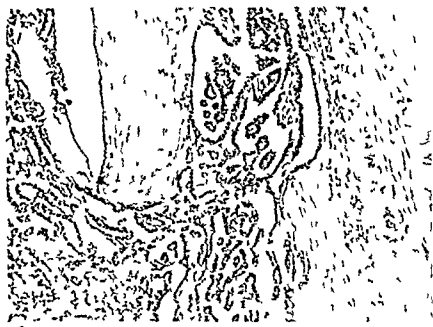


FIG 210—Adenoma of kidney extension through fibrous capsule ($\times 120$)

Many small adenomas show no encapsulation, their marginal elements mingling with the neighbouring renal tubules. Other nodules show thick fibrous capsules but these are rarely if ever complete and at one or more points extensions of the growth through the capsule mingle with the surrounding kidney tissue (Fig 210).

(3) Origin, growth and relationship to carcinoma

From the study of early adenomas it is clear that these arise from the epithelium of hyperplastic convoluted tubules and cysts in damaged kidneys (Stoerk, Nicholson, Newcomb, Trinkle). Continuity of adenomatous epithelium with renal tubules can often be traced and the genesis of the growths appears clearly to involve progressive transformation of tubules into tumour, a process which accounts largely for the intermingling of tumour and renal tissue. Whether adenomas are truly neoplastic from their inception or whether they arise first as focal compensatory hyperplasias which later become neoplastic it is difficult

of renal adenocarcinoma by subcutaneous injections of β anthraquinoline (Semproni and Morelli, Chapter 4) supports the suspicion, plausible also on general grounds, that cancer of the kidney may be due to absorbed chemical carcinogens acting selectively on the renal epithelium during their excretion. Close scrutiny of the occupational, dietetic, and drug histories of victims of the disease might lead to discovery of such carcinogens. The higher incidence of renal cancer in males increases the suspicion of occupational factors in causation.

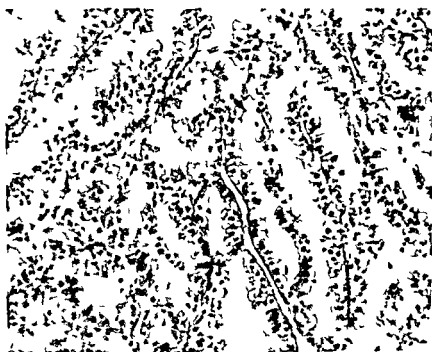


FIG. 211—Clear-celled carcinoma, well differentiated tubules ($\times 120$)

(2) Gross structure and growth

(a) *Naked eye appearances*

The naked eye appearances of renal carcinomas are too well known to need description. Their seeming circumscription and expansive lobular appearance, their variable bulk from small adenoma like tumours to huge masses weighing many pounds, their yellow or orange colour rendered all the more variegated by areas of fibrosis, necrosis, haemorrhage and cystic changes, and their grossly polypoid invasion of the renal pelvis and of main veins are all familiar features. Parts of the tumours which consist, not of the characteristic clear cells, but of more anaplastic cellular growth or of solid celled papillary adenocarcinoma, appear white and white and orange yellow areas often occur in one tumour. Cysts often arise irregularly from degeneration or haemorrhage, but in other cases they are an integral part of the habit of growth of the particular tumour, parts or the whole of which may assume a regular honey combed or polycystic pattern. Such cysts may attain large sizes and thick fibrous walls, in which calcification visible in skiagrams may occur.

cases was 58 years. The disease is rare under 30, my youngest cases were 29, 30 and 32 years of age. Nicholls reported clear celled papillary adenocarcinoma in an infant of 22 months.

(c) *Sex*

In almost all recorded series there is an excess of males over females, the ratio ranging between 3:2 and 5:1. Thus Newcomb's necropsy cases comprised 19 men and 5 women, and mine 23 men and 4 women.

(d) *Race*

There are no reliable comparative figures, but renal carcinoma occurs in Indians, Chinese, Negroes, and other native races (Cooray, Quinland and Cuff, and other references Chapter 5).

(e) *Site*

Young tumours are invariably situated in the cortex, and the relationships of some large tumours also to the surrounding kidney tissues indicate their cortical origin. The tumours arise in any part of the cortex and the right and left kidneys are affected with about equal frequency. Bilateral growths occasionally occur (Forsythe, Beilin and Neiman) but of course metastasis in one kidney from a carcinoma of the other might simulate bilateral new growths. Exley and Hotchkiss reported carcinoma in a supernumerary kidney.

(f) *Renal carcinoma and adenoma in animals*

Nicholson (1913) described a transplantable carcinoma of the rat's kidney and gave references to reports of renal tumours in mice. Renal carcinoma also occurs occasionally in dogs (Feldman, Haigler). I have examined a renal carcinoma from a dog in which both primary growth and metastases in lymph glands and lungs showed well differentiated papillary structure and granular calcification and closely resembled the cortical adenomas of the human kidney. Renal adenocarcinomas resembling those of human beings occurred in several rhesus monkeys in one family described by Ratcliffe. Nieberle and Cohrs depicted a large adenoma of the kidney of a horse and stated that such tumours often attain a huge size, may be papillary or cystic and may become carcinomatous. The renal adenocarcinomas of frogs studied by Lucke were referred to in Chapter 6. (For the embryonic renal tumours of pigs, rats, rabbits and birds see Chapter 60.)

(g) *Causative factors*

Save for the clear relationship of carcinoma to adenoma and for the almost invariable origin of the latter as hyperplastic foci in damaged kidneys, nothing is known of the causation of renal carcinoma. Carcinoma in a granular kidney is often associated with adenomas of other parts of the kidney. It is probable that only some carcinomas arise from pre-existing adenomas, for in only a proportion of cases do cancerous kidneys show evidence of nephritis or arteriosclerosis such as usually accompany adenomas. The experimental production

parts of clear celled tumours This is probably the most healthy type of differentiated structure, and the lipoid accumulation in the more abundant clear-celled



FIG 213 —Clear celled carcinoma primary growth in kidney from same case as Fig 218 ($\times 120$)



FIG 214 —Clear celled carcinoma trabecular pattern in a subcutaneous metastasis in the arm ($\times 120$)

areas is to be regarded as a degenerative process comparable with the lipoid change in the renal epithelium in other pathological conditions, e.g. in chronic

and
ence,
ing

(b) *Invasion of main veins*

Invasion of main veins is frequent and can be found if searched for in the majority of cases. Elsewhere (Willis 1934) I have given references to many examples of intravenous spread of renal carcinomas which in some cases have extended up the inferior vena cava into the right chambers of the heart (Polayes and Taft). McDonald and Priestley have given good illustrations of venous invasion and have shown how this influences prognosis.

(3) *Microscopic structure*

The microscopic structure of renal carcinomas (Figs 211-216) is very diverse including the following variants

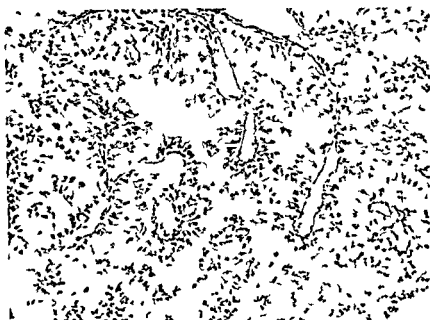


FIG. 212.—Clear-celled carcinoma—tubular and papillary structure ($\times 120$)

(a) Most distinctive of course is the vacuolated or *clear celled type of growth* which is characteristically found in the healthy orange yellow parts of the tumours and which may permit prompt identification of the nature of a tumour from a glance down the microscope. This clear celled type of growth may show distinct tubular or papillary glandular structure or it may be compressed together and devoid of recognizable lumina presenting in section the appearance of plant tissue. Thorough search however will disclose glandular formation in parts of most tumours. The clear celled appearance is an artefact due to the presence in the cells of quantities of doubly refracting lipid material which is dissolved out by the fat solvents used in preparing paraffin sections but which is readily demonstrated in frozen sections or extracts of fresh tumour tissue. Glycogen also is present in the clear cells.

(b) *Solid celled papillary adenocarcinoma* reminiscent of the common form of structure of the renal adenomas is less plentiful but is often to be found in

pathologists, has been specially discussed and exemplified by Loening, Schminke, Brandt, Schaffhauser, and Willis (1932)

(d) *Highly vascular and haemorrhagic tumours* also used to be a source of confusion in histological diagnosis. Haemorrhages into tubular or cystic glandular structures are very common, and produce appearances which were thought to denote a vascular origin of the growths, to which such names as 'perithelioma', 'endothelioma' and 'angio sarcoma' were applied. There is, of course, no justification for such mistakes nowadays.

It is important to recognize that these several varieties of structure do not denote different types of tumour, but are often to be found together, in varying proportions, in individual tumours. The more thoroughly the tumours are examined the more fully it will be appreciated that sub division of the group is unjustified, and indeed impracticable.

(4) Histogenesis

To anyone familiar with the structure of renal carcinomas and adenomas it seems incredible that Grawitz's hypothesis of their adrenal origin can have survived to the present day, as, for example, in MacCallum's text book (1942). This hypothesis based on no more than a very superficial resemblance of parts of renal tumours to adrenal cortical tissue, should have become permanently obsolete in 1908 when Stoerk's complete refutation of it appeared. But, like many other already exploded hypotheses it has suffered ill advised revivals in spite of repeated exposure of its falsity by Zehbe, Glynn, Ipsen, Wright, Nicholson, Derrick, Inglis and Jones and many others.

I do not propose to enumerate the many objections to the Grawitz hypothesis, the falsity of which I think should be sufficiently clear from the structure of the tumours alone. Those interested in further details of the controversy—one which has claimed far more attention than it merits—will find all they need in the papers just cited. My own opinion is well expressed in Nicholson's words: 'For me the controversy was settled by Stoerk, and finally buried by Glynn, and the suprarenal origin of the hypernephromata disproved.' To which I would add that I find it incomprehensible that any serious student of the subject, or indeed even an unbiassed beginner properly examining a few typical specimens of renal carcinomas and adenomas, could reach any other conclusion. Carrying as it does such objectionable implications, the name 'hypernephroma' should be discarded.

(5) Metastases

Renal carcinomas are very fickle and unpredictable in their behaviour. Some grow for long periods and to huge sizes without yielding metastases, others remain small and symptomless, yet produce large remote metastases usually by the blood stream. Metastatic growths have caused many errors of diagnosis (Willis, 1934. Trinca and Willis), and these growths sometimes appear in unusual situations, such as the skin, muscles, tonsil, oral or nasal mucosa, larynx, iris, fingers etc. Following nephrectomy metastatic growths may soon appear in the lungs, bones or elsewhere or they may not appear until 6, 8 or 10 years later, as in cases reported by Clairmont, Albrecht, Fischer and Broster.

hydraemic nephritis. Some carcinomas are predominantly of solid celled type usually however with some clear celled areas

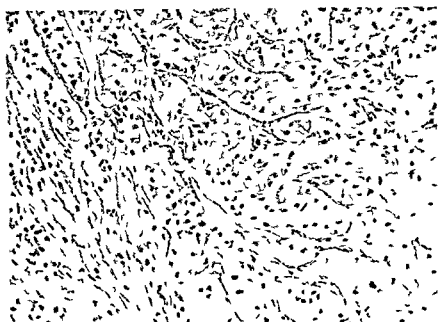


FIG 215—From a metastasis in the myocardium in the same case as Fig 214 ($\times 120$)

(c) *Anaplastic variants* spindle celled or pleomorphic celled and often diffuse and sarcoma like in appearance, have led to many erroneous diagnoses of



FIG 216—Solid-celled carcinoma unusually discrete distribution of tubular structures in oedematous stroma ($\times 120$)

sarcoma carcino-sarcoma or mixed tumour of the kidney. The structural versatility of renal carcinoma still insufficiently appreciated by many

Other sites of clinically obtrusive metastases include the skin or subcutaneous tissues (Halstead , McNathin and Dean , Smyth , Deuticke , Busser , Bungeler and

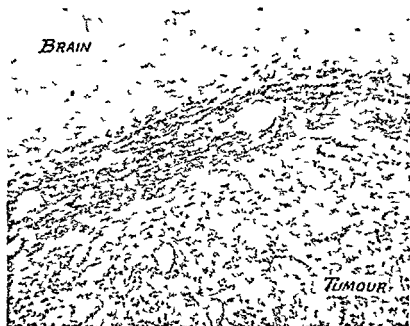


FIG 217 —A prominent zone of fibrin at the margin of a metastasis of clear-celled carcinoma in the brain ($\times 40$)

de Castro), the external auditory meatus (Benesi), the oral cavity (Coenen , Willis, 1931, Case 13 , and see Figs 218 and 213 from case reported by Trinca and

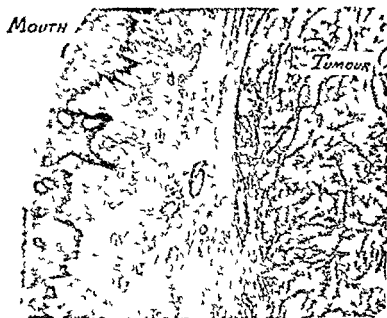


FIG 218 —Metastasis of clear-celled carcinoma in floor of mouth from same case as Fig 213 (see Trinca and Willis (1936) Case 14) ($\times 40$)

Willis 1936) the larynx (Turner), the thyroid (Deuticke , Willis 1934, Case 188) the choroid or iris (Chance Kreisbig Hudson and Lister)

Perhaps more often than any other tumour renal carcinomas produce solitary metastases in bone brain or other tissue (Albrecht, Scudder, Lehmann), and it has been claimed that surgical removal of both primary and secondary growths is sometimes curative in such cases (Smyth), a claim which it need scarcely be said, should not be made until there has been prolonged post operative freedom from recurrence

(a) *Metastases in lymph glands*

Deposits of growth are present in the lumbar lymph glands in about one half of necropsy cases. The glands regional to metastasis-containing organs also often contain growth especially the hilar glands when the lungs are affected. Invasion of the thoracic duct occurs occasionally, e.g. in Winkler's Case 10 and Schwedenberg's Case 7.

(b) *Blood borne metastases*

The frequency of metastasis by the blood stream is explained by the proneness of renal cancer to invade veins, and examination of surgically removed kidneys for venous invasion is important in individual prognosis. The main sites of metastasis were exemplified in my series of 10 cases reported in 1941 in which metastases were present in the lungs in 8 cases (and in an additional case microscopic intravascular tumour emboli were present), in the liver in 5, bones 4, opposite kidney 4, brain 3, thyroid 3, myocardium 2, adrenal 2, pancreas 1 and subcutaneous tissue 1 case. Metastatic tumours like primary ones often show a proclivity to invade main veins (Fig. 36).

The lungs contain metastases in at least three quarters of fatal cases and miliary metastases have been mistaken both clinically and radiographically for tubercles (Huguenin and Delarue). The liver contains deposits in about one half of fatal cases. Trinca and I (Case XV) described a case in which exploratory operation for suspected gall bladder disease with jaundice revealed invasion and occlusion of the common bile duct by a secondary growth.

The skeleton is a favourite site of metastases which are present in nearly one half of necropsy cases. In my 1934 work I gave references to many cases in which metastases had simulated primary diseases of bone a subject specially discussed also by Rost, Gibson and Bloodgood, Joll, Deuticke and Lehmann. Unusual sites of metastasis include the clavicle (Rost), metacarpals (Fabre and Dambrin), phalanges (de Massary and Weil) and jaws (Esau, Stein, Branch and Norton). The metastases are osteolytic and destructive often causing pathological fractures and often invading surrounding soft tissues. The tumours may show pulsation and may be mistaken for aneurysms (Eshner).

The brain contains metastases in about one quarter of fatal cases. Renal carcinoma is third on the list of primary tumours most commonly responsible for secondary growths in the brain being exceeded in this respect only by carcinomas of the breast and lung. Cerebral metastases may produce the main or only symptoms and so may cause misdiagnosis as in cases referred to in my 1934 work. A conspicuous zone of fibrin may develop around metastases of renal carcinoma in the brain (Neuburger and Singer and Fig. 217).

466 ADENOMA AND CARCINOMA OF THE KIDNEY PARENCHYMA

- LEHMANN, W (1932) 'Hypernephrommetastasen des Skelettsystems', *Arch klin Chir*, 170 331 (An excellent review)
- Loening F (1908) *Beitr path Anat* 44 17
- MANASSE, P (1896) 'Zur Histologie und Histogenese der primären Nierengeschwülste' *Virchows Arch* 143 278
- MANASSE, P (1896) *Ibid* 145 113
- de Massary E and Weil P (1907) *Bull Soc med Hôp, Paris* 24 1456
- MacCallum W G (1942) *A Textbook of Pathology* p 1104 Philadelphia
- McDonald J R and Priestley J T (1943) *Surg Gyn Obst* 77 295
- McNathun R F and Dean A L (1931) *Amer J Cancer* 15 1570
- Neuburger K and Singer L (1925) *Virchows Arch* 255 555
- NEWCOMB, W D (1936) 'The origin of Grawitz tumours of the kidney' *Proc Roy Soc Med* 30 113
- Nicholls M F (1936) *Proc Roy Soc Med* 29 372
- Nicholson G W (1913) *J Path Bact* 17 329
- NICHOLSON, G W (1923) 'The hypernephromata', *Guy's Hosp Rep* 73 164 (The best account of the Grawitz controversy)
- Nieberle K and Cohrs P (1931) *Lehrbuch der Spez Path Anat der Haustiere* p 522 Jena
- Polayes S H and Taft, H (1931) *Amer J Path* 7 63
- Ratcliffe H L (1940) *Amer J Path*, 16 619
- Rost F (1912) *Virchows Arch* 208 53
- Schaffhauser F (1929) *Z Krebsforsch* 28 131
- SCHMINCKE, A (1923) 'Ueber den sarkomähnlichen Bau der Grawitz schen Tumoren der Niere' *Zbl allgem Path (Fest)* 33 264
- Schwedenberg T (1905) *Virchows Arch*, 181 295
- Scudder C L (1906) *Ann Surg* 44 851
- Scudder C L (1910) *Ibid* 52 533
- Smyth M J (1939) *Brit J Surg* 27 266
- Stein G (1929) *Dtsch Z Chir* 219 318
- STOERK, O (1908) 'Zur Histogenese der Grawitz schen Nierengeschwülste', *Beitr path Anat* 43 393 (A classical well illustrated paper proving the renal origin of the Grawitz tumours)
- Sudeck P (1893) *Virchows Arch* 133 405
- Sutter H (1902) *Virchows Arch* 168, 305
- Trinea A J and Willis R A (1936) *Med J Austral* ii 222
- TRINKLE, A J (1936) 'The origin and development of renal adenomas and their relation to carcinoma of the renal cortex (hypernephroma)', *Amer J Cancer* 27 676
- Turner A L (1924) *J Laryng* 39 18
- Willis R A (1931) *Med J Austral*, i 653
- Willis R A (1932) *Ibid* ii 65
- Willis R A (1934) *The Spread of Tumours in the Human Body*, pp 15, 192 194 and 431 London
- Willis R A (1941) *Med J Austral* ii 258
- Winkler K (1898) *Virchows Arch* 151 (Suppl.) 195
- WRIGHT, H W S (1921) 'A study of the surgical pathology of hypernephromata' *Brit J Surg* 9 338
- ZEHBE, M (1910) 'Untersuchungen über Nierengeschwülste', *Virchows Arch*, 201, 150 (Another good account refuting Grawitz)

✓ (c) *Retrograde venous metastasis to the genitalia*

This deserves special comment. Tumour invasion of the spermatic or ovarian veins which of course is much more common from tumours of the left kidney than from those of the right may be followed by retrograde tumour embolism of the pampiniform or ovarian plexus or the parametrial or vaginal veins, and the development of secondary growths in the spermatic cord epididymis parametrium, vagina or vulva. Metastases of this kind in women have been described by Gellhorn, Hirsch Hoffmann, Fleischmann Gragert, and others and in men by Sutter and Derman. In several cases the vaginal or vulval growths have been the first signs of disease. Begg described a case in which priapism due to secondary deposits in the erectile tissue was the main symptom of renal carcinoma.

REFERENCES

- ALBRECHT, P (1905) Beiträge zur Klinik und path. Anatomie der malignen Hypernephrome *Arch. klin. Chir.* 77 1073
 Begg R C (1928) *Brit. Med. J.* ii 10
 Beilin L M and Neiman B H (1942) *J. Urol.* 48 575
 Benesi (1914) *Berlin klin. Wschr.* 51 378
 Branch C I and Norton R H (1928) *New Engl. J. Med.* 198 559
 Brandt M (1927) *Virchows Arch.* 264 677
 Broster L R (1923) *Brit. J. Surg.* 11 287
 Broster L R (1929) *Proc. Roy. Soc. Med.* 23 551
 Bungeler W and de Castro A M (1939) *Virchows Arch.* 303 570
 Busser F (1934) *Ann. Anat. path.* 11 412
 Chance B (1907) *J. Amer. Med. Assoc.* 48 475
 Clairmont P (1904) *Arch. klin. Chir.* 73 620
 Coenen H (1914) *Berlin klin. Wschr.* 51 1626
 Derman G L (1927) *Virchows Arch.* 265 304
 Derrick E H (1922) *Med. J. Austral.* i 623
 Deuticke P (1931) *Dtsch. Z. Chir.* 231 767
 Esau J (1925) *Med. klin.* 21 1086
 Eshner A A (1903) *J. Amer. Med. Assoc.* 50 1787
 Exley M and Hotchkiss W S (1944) *J. Urol.* 51 569
 Fabre P and Dambrin P (1935) *Ann. Anat. path.* 12 380
 Feldman W H (1932) *Neoplasms of Domesticated Animals* p 303 Philadelphia
 Fischer B (1910) *Munch. med. Wschr.* 57 101
 Fleischmann C (1929) *Zbl. Gynak.* 53 1458
 Forsythe W E (1942) *J. Urol.* 47 784
 Gellhorn G (1918) *Amer. J. Med. Sci.* 156 94
 Gellhorn G (1929) *Zbl. Gynak.* 53 527
 Gibson A and Bloodgood J C (1923) *Surg. Gyn. Obst.* 37 490
 GLYNN E E (1912) The adrenal cortex: its rests and tumours etc. *Quart. J. Med.* 5 157
 (Refutes Grawitz's hypothesis)
 Gragert O (1929) *Arch. Gynak.* 136 167
 Hargler S W (1943) *J. Amer. Vet. Med. Assoc.* 102 469
 Halstead A E (1907) *Surg. Gyn. Obst.* 4 654
 Hirsch Hoffmann H U (1928) *Zbl. Gynak.* 52 1970
 Hudson A C and Lister W (1934) *Proc. Roy. Soc. Med.* 27 1613
 Huguenin R and Delarue J (1930) *Ann. Anat. path.* 7 524
 Inglis K and Jones E B (1930) *J. Coll. Surg. Austral.* 3 225
 IPSEN J (1912) Untersuchungen über die Grawitz'schen Geschwülste. *Beitr. path. Anat.* 54 233 (A good account refuting Grawitz's hypothesis)
 JOLL, C A (1923) Metastatic tumours of bone. *Brit. J. Surg.* 11 78
 Kreisig W (1931) *Z. Augenheilk.* 75 326

tumours do not favour any special part, but in the *ureter* the lower part is the most often affected. For good accounts of the renal pelvic and ureteric growths, see the papers of Spiess Mecker and McCarthy, Scholl (1924), Bissell, Stewart Rousselot and Lamon, D Aunoy and Zoeller, Renner, and Kimball and Ferris.

The following is a noteworthy case of annular stenosing carcinoma of the ureter.

Case I—Male aged 60. Clinical diagnosis: pyelonephritis. *Necropsy* revealed a small annular stenosing growth at the junction of the middle and lower thirds of the right ureter. The pyonephrotic renal pelvis showed pronounced leucoplakia but the ureter near the growth was unaffected. No metastatic growths were found. *Histology*—Diffusely infiltrating squamous-cell carcinoma of the ureter, advanced squamous metaplasia with much keratinization of the renal pelvis.



FIG. 219.—*Case II*. Carcinoma of ureter. A = closely packed narrow papillary structure. B = more bulky epithelial masses with atypical areas. ($\times 60$)

✓(4) Multiplicity

In a large proportion of cases the tumours are or become multiple, e.g. in 250 of the 902 cases of carcinoma of the bladder recorded by Kretschmer *et al*. Tumours of the renal pelvis are often accompanied or followed by tumours of the corresponding ureter or of the bladder, this association being the special subject of Kimball and Ferris's review. In 74 instances of this kind, the sites of the multiple tumours associated with main growths in the renal pelvis were the ureteric orifice and its immediate neighbourhood in 48 per cent of the cases, the ureteric orifice and other parts of the bladder as well in 36 per cent, the bladder only in 14 per cent, and the ureter only in 2 per cent.

The following is an unusual example of simultaneous massive carcinoma of the pelvis of the kidney and of the lower part of the ureter.

CHAPTER 28

EPITHELIAL TUMOURS OF THE URINARY PASSAGES

ALTHOUGH regional grouping of the tumours of the urinary passages, namely of the renal pelvis ureter and bladder, is important to the clinician in diagnosis and treatment, it is of less interest to the pathologist for these passages are lined throughout by an identical transitional stratified epithelium, the tumours of which in all situations show a similar range of structure and behaviour and almost certainly have a similar aetiology. Further, although it is customary, and for clinical purposes useful to distinguish between benign papillomas and carcinomas of the urinary tract epithelium it is impossible to make any real pathological distinction between them. Here more than in any other situation, there occur tumours showing every possible gradation and every possible sequence from solitary highly organized non invasive papilloma to disorderly invasive carcinoma. Any sub division of the whole group is necessarily arbitrary, and in this chapter therefore it is treated as a whole. Certain rare tumours of special origin—those of the urachus and of the urethra and its glands—are dealt with separately at the end of the chapter.

SEX AGE, SITE AND SPECIES INCIDENCE

(1) Sex

Men are affected more commonly than women in the ratio of about 3 to 1 in most series, as in the 902 cases of carcinoma of the bladder in the registry of the American Urological Association (Kretschmer *et al*) and in the 74 cases of papillary growths of the renal pelvis collected by Kimball and Ferris. My necropsies comprised 37 cases of vesical carcinoma of which 27 were in men and 8 cases of renal pelvic and ureteric carcinoma all but one of which were in men, giving a total of 34 men and 11 women.

(2) Age

The age distribution peak is early in the seventh decade. More than half of the cases occur between the ages of 50 and 70. The tumours are rare under 30 e.g. in only 5 of 902 cases of vesical cancer (Kretschmer *et al*). The mean age at death of my 37 cases of carcinoma of the bladder was 64 and of my 8 cases of carcinoma of the renal pelvis or ureter 60.

(3) Site

The tumours occur in the bladder, renal pelvis and ureter in that order of frequency. This is probably related in a large measure at least merely to the relative areas of mucous membrane in the three parts. In the bladder more than three quarters of the tumours arise on the lateral walls near the ureteric orifices or on the trigone or neck, while the posterior wall, fundus and anterior wall are the least frequent sites (Kretschmer *et al*). Tumours in diverticula are seen occasionally as in the case depicted by Scholl (1944). In the renal pelvis the

mucosa, and (d) the general analogy with multiple tumours in other epithelial organs, e.g. multiple polyposis in the colon, multiple papillomas in the mammary ducts or multiple carcinomas of the skin, in which multicentric origin is unequivocal. The arguments favouring urinogenous metastasis are (a) the 'secondary' tumours usually appear, not fortuitously in any other part of the urinary tract but in relation to the initial tumour, e.g. in the corresponding ureter or bladder in cases of growth in the renal pelvis, (b) intervening parts of the mucosa may appear quite healthy and devoid of any signs of a pre-cancerous state such as might suggest a general instability of the whole urinary tract epithelium, and (c) there is evidence that even extra urinary tumours may occasionally implant themselves within the urinary passages (see Böger's case cited in Chapter 10). The weight of the evidence seems to me to point to multicentric origin as being a much more important factor than urinary metastasis.

(5) Urinary tract tumours in animals

Feldman (1932, Chapters XVII-XIX) and Nieberle and Cohrs (1931, p. 535) mention examples of papillomas and carcinomas of the bladder in horses, cattle and dogs. Schlotthauer recorded two examples of squamous cell carcinoma of the bladder and Stalker and Schlotthauer an example of squamous cell carcinoma of the female urethra, in dogs. Langham *et al.* described multiple mucus-secreting papillary adenomas of the bladder in cows.

POSSIBLE FACTORS IN CAUSATION

(1) Aniline tumours of the bladder

The only clear instance of an occupational incidence of urinary tract tumours is in workers with aniline dyes. Attention was first called to this in 1895 by Rehn who recorded several cases of vesical cancer in fuchsine workers. A symposium by Ferguson, Gay and others in 1934 reviewed knowledge of the subject, while Hueper's paper (1938) and Chapter V of his book (1942) give admirable accounts of more recent clinical and experimental work. Thanks to the latter, the carcinogenic properties of β -naphthylamine have been proved, and there seems little doubt that this substance is the main, though perhaps not the only, carcinogen responsible for aniline tumours of the bladder. Other aromatic amines deserve study in this respect, and it should also be recalled that some other compounds, e.g. several azo dyes and acetylaminofluorene, have selective carcinogenic effects on the urinary tract. It is quite possible, as Davis urged, that some of the many dyes ingested in confectionery cordials and foods, or absorbed from cosmetics, as well as those used in industry, are responsible for some of the urinary tract tumours in man.

(2) Schistosomiasis and urinary tract tumours

The many reports of carcinoma of the bladder associated with bilharzial infection have all come from Egypt. Valuable accounts include those of Ferguson and Dolbey and Moor, and Hueper (1942) has given a useful review of the subject. Caution is needed however, before assuming that the parasite is the essential cause in these cases. Almost all the reported cases have been in

Case II—Female aged 64. Routine medical examination disclosed a palpable right abdominal tumour. Operative removal of the enlarged right kidney and ureter was performed the latter distended in its lower part by a cylindrical mass of growth which was cut across during removal. Cystoscopic examination however showed that the ureteric growth did not project into the bladder. *The specimen*—The kidney was much enlarged and consisted of a thick shell of white growth around a ragged central cavity with no residual kidney tissue visible. The removed portion of ureter was 12 centimetres long its upper half was patent and contained no growth its lower half was occluded and distended by a cylindrical mass of growth 1.5 centimetres in diameter. *Microscopy* (Fig. 219) showed papillary carcinoma of typical urinary tract type still largely confined within the renal capsule and ureter but with invasion of the wall at some places.



FIG. 220—*Case III* Papillary carcinoma of bladder ($\times 60$)

The following case exemplifies multiple growths in the bladder

Case III—Male aged 82 with dysuria for many months attributed to prostatomegaly. *Necropsy* showed the bladder to be distended by a shaggy mass of growth 10 centimetres in diameter which however consisted of 8 separate pedunculated tumours with unaffected intervening mucous membrane. The attachments of most of the tumours were on the lateral walls above the trigone the ureteric orifices were not involved. There were no metastases. *Histology* (Fig. 220)—Papillary carcinoma of typical urinary tract type with little or no invasion of the muscle coat.

Multiplicity of tumours in the urinary tract has been attributed by some workers to implantation metastasis and by others to multifocal tumour formation. While metastasis by implantation in the urinary passages must be admitted as possible and even is probable in some cases (see Chapter 10 and Willis 1934) it is clear that multifocal origin also often occurs. In favour of multifocal origin are (a) the cystoscopic appearance of early multiple tumours in the bladder (b) the microscopic structure of early growths which often show clear signs of genesis from the stratified epithelium still in progress (c) the improbability of detached tumour particles in the urine successfully grafting themselves on intact

as in Case I above. Probably only occasional tumours take origin from previously leucoplakic epithelium. Squamous change in carcinomas of the urinary passages is usually a metaplasia in the tumour tissue itself, and does not denote that the tumours have been preceded by metaplasia.



FIG. 221.—Brunst's nests in chronic pyelitis. The largest nest in B shows early lumen formation ($\times 100$).

(5) Other inflammatory diseases

Ewing's opinion that cystitis precedes carcinoma in a high proportion of cases is not in accord with clinical experience. Surgeons with whom I have discussed the question are unanimous that in most cases of tumour the first symptoms of urinary disease are those caused by the tumour itself, and Kretschmer *et al* found no evidence of any pre-cancerous lesions in their large series of cases. There is no evidence that people with chronic obstruction of the urinary tract from strictures, prostatic enlargement, tuberculosis or other causes are predisposed to cancer. Renal or vesical calculi are found associated with tumours of the renal pelvis or bladder in about one quarter of the cases, but it is clear that in most of these cases the calculi are secondary to the tumours and of no causative

Egyptians or Egyptian Arabs, amongst whom bilharzial disease is very prevalent, as much as 90 per cent of the population being infected in many districts. Hence it is inevitable that a high proportion of cases of urinary tract cancer in these people will be accompanied by the parasite even if no causative relationship exists between the two diseases. The evidence advanced that there is some causative relationship includes (a) estimates which appear to show that Egyptians with schistosomiasis have a higher incidence of vesical cancer than Europeans and other non infested peoples, and (b) the occasional occurrence of vesical cancer in Europeans with chronic schistosomiasis, as in the case reported by Fairley. As to (a), we must recall that estimates of the relative frequencies of particular diseases contain many potential fallacies, especially in hospital material which is often selected in various ways and that comparisons of the incidence of a given tumour in different countries especially when these differ widely in their standards of medical practice and registration are very hazardous (see Chapter 5). As to (b) cases of this kind are too few to warrant any deductions. In my opinion then while it is quite possible that bilharzial cystitis does indeed predispose to carcinoma the evidence is still not wholly conclusive and further careful statistical and pathological investigation is needed.

(3) Carcinoma in exstrophy of the bladder

There is little doubt that exstrophy predisposes to carcinoma of the bladder. McCown collected records of 25 cases of carcinoma of the exstrophied bladder, and Abeshouse also gave a useful review of the subject. Of the 27 tumours reviewed 21 were adenocarcinomas, a proportion in striking contrast to that for carcinomas of the normally situated bladder, only 2 per cent of which are adenocarcinomas. As shown by Patch and Rhea and by Abeshouse cystic and glandular metaplasia is prominent in the exstrophied bladder, and it is the metaplastic epithelium which is predisposed to cancerous change. Carcinoma of the exstrophied bladder is most often situated in the upper part. It has the same sex incidence as vesical cancer in general, but may appear at rather earlier ages. Abeshouse's review comprised 17 men and 9 women of ages ranging from 23 to 66 years the greatest number (7) being in the fifth decade. Metastases have not been reported.

(4) Metaplastic inflammations

(a) *Cystitis pyelitis or ureteritis cystica and glandularis*

This occurs not only in the exstrophied bladder but also in the normally situated organs as first described in 1893 by Brunn and later by Stoerk Stow Wilson Patch and Rhea and Abeshouse. All stages in the formation of Brunn's nests, tiny cysts and mucus secreting glands can be traced and there seems no doubt that these changes predispose to adenocarcinoma. The precise factors responsible for metaplasia of this type are still unknown. Fig 221 depicts Brunn's nests in a hydronephrotic kidney of a man of 52 years, the whole pelvic mucosa was similarly affected.

(b) *Leucoplakia*

Leucoplakia of the urinary passages is seen in association with chronic tuberculous or calculous disease or with carcinoma, in a small proportion of cases.

confined within the walls of the pelvis, ureter or bladder before invasion of surrounding tissues supervenes

(c) *Cornifying squamous cell carcinoma* (Fig 225)

This is a frequent structural variant in part or whole of many invasive tumours. Not uncommonly the superficial parts of a tumour consist mainly of papillary growth of type (b), while its deeper invasive parts are epidermoid



FIG 223 —Villous papillary carcinoma of bladder showing cellular pleomorphism ($\times 80$)

(d) *Anaplastic invasive carcinoma*

This includes spheroidal celled, diffuse pleomorphic celled (Jolly) and a haemorrhagic type resembling chorion epithelioma (Venulet). There is little doubt that many supposed "sarcomas" of the bladder have been of this kind.

Again it must be insisted that these are not distinct kinds of growth. All gradations are seen and several or all of the structural variants may occur in one tumour.

(e) *Mucoid adenocarcinoma*

This type, well reviewed by Abeshouse, constitutes about 2 per cent of carcinomas of the bladder. It arises chiefly in the trigone, appears to be related to the condition of *cystitis glandularis* already referred to, and often shows areas of transitional stratified structure as well. It is to be distinguished from mucoid urachal carcinoma (see below) which arises at the apex of the bladder and is said to be purely glandular in structure. Most carcinomas of the exstrophied bladder are adenocarcinomas. Govan described a benign mucus-secreting cystadenoma of the bladder.

significance. The rare condition of malakoplakia seen in some cases of chronic cystitis, well described by McDonald and Sewell and Chisholm and Tudhope apparently does not predispose to tumour. The suggestion of Kirwin that urinary papillomas may be due to a virus is purely speculative.

STRUCTURE AND GROWTH

Of the *gross appearances* of the tumours which are plentifully illustrated in many papers and text books I propose to say little. Gay's brief description of the "aniline tumours" applies equally well to those of undetermined causation.

The tumours are single or multiple, papillary or sessile, infiltrating or non-infiltrating, ulcerating or non-ulcerating, or there may be any combination or sequence of these characteristics.



FIG. 222.—Well differentiated villous papilloma of bladder ($\times 120$)

(1) Microscopic structure

The following types of structure are found

(a) *Highly organized villous papillary growth* (Fig. 222)

This consists of a uniform layer of typical transitional stratified epithelium closely resembling that of the normal urinary tract clothing delicate vascular connective tissue papillae. This is the structure of the typical benign papilloma.

(b) *Less highly organized papillary growth* (Figs. 219, 220, 223, 224)

This shows epithelium still of urinary tract type but more bulky, less regular, including solid masses with little or no papillary arrangement and showing many mitotic figures. This is the structure of most papillary carcinomas. Invasive properties may be much or little in evidence; many of the tumours long remain

recurrences are apt to assume increasingly dangerous characters and to terminate eventually in invasive growth and metastasis. This sequence has been well described by Kretschmer *et al.*, who found that in 38 per cent of cases with multiple vesical tumours, there was a history extending over a period of 5 years or longer in one case for 49 years, with repeated recurrence often terminating in frank carcinoma. They described the history of a typical case of this kind terminating in metastasis 13 years after initial removal of a "benign" tumour.

The disease apparently originates in multiple foci in the bladder mucosa, appears first microscopically benign and may continue to appear so on repeated biopsy for years. From time to time new tumors will be found and if accurately observed it can be definitely shown that there is no recurrence in previously treated areas and that the new tumors represent true new growths and not recurrences.

In spite of the apparent benignity of the tumor under the microscope, the disease may infiltrate the lymphatics and metastasize or infiltrate nearby structures. The entire course of events may be spread over a period of from 5 to 20 years. Some multiple tumors are clinically malignant, no matter how benign the tissue may appear under the microscope.

From the point of view of their behaviour and prognosis, urinary tract tumours might conveniently be grouped into the following 3 groups:

- (i) Solitary tumours of "benign" structure, some of these are cured by local removal, others are the forerunners of multiple recurrent growths.
- (ii) Recurrent multiple growths of "benign" structure comprise the dangerous group just discussed, though of long duration the disease is not permanently cured by local removal of individual tumours, and unless radical removal of the whole tumour bearing field can be carried out it will eventually terminate fatally.
- (iii) All other solitary or multiple growths of frankly cancerous or of atypical structure when first discovered, run a more rapid malignant course, and, unless radically removable, end fatally in a few months or years.

METASTASIS

Many papillary growths, even though structurally atypical in parts remain confined to the mucous membrane for long periods before they show invasive properties. The metastasis of such tumours outside the urinary system is long delayed, so that, if operative removal is possible, such as nephrectomy for renal pelvic growths and if multiple tumours do not develop later in other parts of the urinary tract, cures are sometimes obtained. With invasive carcinoma, however, metastasis to regional lymph glands or by the blood stream occurs early, as in cases of renal pelvic carcinoma described in my 1941 paper and cases of ureteric carcinoma reported by Jolly. Invasion of veins, as depicted by McDonald and Priestley, is the prelude to haemic metastasis.

(a) *Metastases in lymph glands*

These are present in about one third of fatal cases, e.g. in 14 of my 45 necropsies. In my Case 217 enlarged glands in the neck were the first signs of disease and led to a false diagnosis of Hodgkin's disease, and in Case 228 the cisterna chyli and thoracic duct were cancerous.

(2) Duration , change of structural type , prognosis

While some solitary papillomas are permanently cured by local removal the prognosis of any case of urinary tract tumour is uncertain. This is because



FIG 224 —Pulmonary metastasis of the tumour of Fig 223 showing similarity of structure ($\times 80$)



FIG 225 —Epidermoid carcinoma of renal pelvis ($\times 80$)

recurrence by multiple tumour formation occurs in a considerable proportion of cases initially regarded as benign and because with the lapse of time repeated

CARCINOMA OF THE MALE URETHRA

This is a rare disease. In 1925 Diehl reviewed 61, and in 1939 Kreutzmann and Colloff 148, reported cases. Of these 148 cases, 56 were in the fifth decade, the age range being 18 to 91 years. There was a history of stricture—gonorrhoeal or traumatic—in three quarters of the cases. The site of the tumours is in the bulbo membranous slightly more frequently than in the penile part of the urethra, and rarely in the prostatic part.

(1) Structure and growth

In the great majority of cases the tumours are cornifying squamous cell carcinomas, and only occasionally papillary growths of transitional urinary tract type or adenocarcinomas, the latter doubtless arising from Cowper's or Littre's glands. Deming and Lindskog saw an unusual case in which, over a period of 13 years, multiple recurrent papillary growths of the bladder were followed by similar multiple tumours of the urethra. Usually urethral carcinoma appears as a single growth, which, however, may widely invade the penis, scrotum or rectum and may cause priapism by invasion of the erectile tissue (Ikeda *et al*).

(2) Metastasis

Metastasis takes place to the iliac, pelvic and inguinal lymph glands, which, however, are often found enlarged by inflammation while still free from growth. Metastasis by the blood stream to the lungs, liver, or rarely to other parts may also occur.

CARCINOMA OF THE FEMALE URETHRA

Vulval or vaginal growths not infrequently involve the urethra, but carcinoma of the urethral canal itself is rare. Shaw, Culver and Forster, and Kaufmann give references to reported examples. Both squamous cell carcinoma of the surface epithelium and adenocarcinoma of the urethral glands occur. Caruncles are benign non-neoplastic inflammatory lesions, which rarely, if ever, undergo cancerous change, but they often show atypical areas of proliferating epithelium which can easily be mistaken for carcinoma by the inexperienced.

EPITHELIAL TUMOURS OF THE URACHUS

The urachus, the remnant of the allantois extending from the apex of the bladder to the umbilicus, is not as is often supposed a simple fibrous cord, but nearly always contains residual epithelial cords or small cysts. Begg (1930) made a careful study of these residues, which consist of an irregular form of transitional stratified epithelium, which, however, as age advances, often gives rise to gland-like outgrowths. Carcinomas or benign cystic growths may arise from these residues, the former usually having the structure of mucoid papillary adenocarcinoma (Nuboer, 1925; Begg, 1936; Willis, 1941, Case 383). Distinction of urachal carcinoma from mucoid adenocarcinoma of the bladder itself may

(b) Blood borne metastases

These are present in at least one third of fatal cases, e.g. in 16 of my 45 necropsies the organs most frequently affected being the bones lungs and liver. Metastases in bones, as described by Kretschmer Joll Nicholls Graves and Militzer, are of special frequency and importance. Their distribution in the skeleton is that of metastatic growths generally, their most frequent sites being the vertebrae, ribs, pelvis femur and humerus, but they occur also in the skull, clavicle tibia radius, etc. The changes in the bones are usually osteolytic. Direct non metastatic invasion of the vertebrae or pelvis from the primary growths or their lymph nodal metastases also occurs as in Jolly's cases. The metastases in bones may show a highly differentiated papillary structure as in Nicholls's case in which also the affected bones showed osteoplastic changes.

While blood borne metastases from urinary tract carcinomas usually do not appear until relatively late stages of the disease exceptions to this rule are not unusual. As Kretschmer noted, metastases in bones particularly may develop early from quite small operable primary growths. The following cases exemplify widespread metastasis from small unsuspected primary tumours.

Case IV—Male aged 45. *History*—Increasing anaemia and weakness for some months with palpable enlargement of the liver. Disseminated malignant disease was suspected but no primary growth could be discovered. *Necropsy* disclosed an area of infiltrating growth 1.5 centimetres in diameter at the apex of one of the pyramids of the upper part of the left kidney without gross ulceration into the pelvis and without any visible invasion of renal veins. There were large deposits of growth in many lumbar lymph glands many metastases in the liver extensive diffuse cancerous permeation of the pulmonary lymphatics and alveoli and widespread metastatic deposits in many bones especially the vertebrae and ribs. *Microscopically* the tumour was an anaplastic spheroidal cell carcinoma but with areas showing recognizable differentiation both of urinary transitional and squamous cell type. The rib metastases showed much new bone formation by the expanded periosteum.

Case V—Male aged 64 a diabetic. *History*—Pain in the back and right leg commenced in October 1938 and was diagnosed as sciatica. In April 1939 a large mass involving the right ilium was noticed and skiagrams suggested extensive metastatic growth. *Necropsy* in the same month showed many secondary tumours in the lungs liver and vertebrae a large growth 18 centimetres in diameter replacing the right ilium with much formation of new bone by expanded periosteum (Fig. 25) a thyroid adenoma 2 centimetres in diameter containing a crescentic area of soft white growth 1 centimetre in main extent and a flat area 2 centimetres in diameter of papillary growth replacing the mucosa on the anterior wall of the bladder. The tentative necropsy diagnosis was probable malignant adenoma of thyroid with widespread metastases. *Histology*—The bladder tumour was a papillary carcinoma of typical transitional type slightly infiltrating the muscle coat. The tumours in the lungs liver bones and thyroid were clearly metastases of the vesical tumour showing in parts distinct differentiation of transitional stratified characters with also some cornification. The metastasis in the thyroid lay within an old fibrous partly calcified adenoma.

In my other necropsies I have seen metastases also in the myocardium brain, thyroid kidney and adrenal. It is possible that urinary tract tumours may have a special tendency to metastasize in the heart. Cardiac metastases were present in 5 of Ferguson's 40 cases of bilharzial cancer of the bladder and Keynes saw a single nodule in the heart as the only metastasis of a renal pelvic carcinoma.

- Ferguson R S Gehrman G H, Gay D M Anderson, L W, and Washburn V D (1934) *J Urol* 31 121
- Govan A D T (1946) *J Path Bact* 58, 293
- Graves R C and Miltzer, R E (1934) *J Urol* 31 769
- HUEPER W C (1938) 'Aniline tumors of the bladder' *Arch Path* 25 856 (A valuable review)
- Hueper W C (1942) *Occupational Tumors* p 534 Springfield
- Ikeda K Foley F E B and Rosenow J (1943) *J Urol* 49 732
- Joll C A (1923) *Brit J Surg*, 11 38
- Jolliv A T H (1939) *Med J Austral* 11 576
- Kaufmann E (1929) *Pathology*, p 1454 (Translation by Reimann) Philadelphia
- Keynes G (1924) *Brit J Surg* 12 224
- Kimball F N and Ferris H W (1934) *J Urol* 31, 257
- Kirwin T J (1943) *J Urol*, 49 1
- Kretschmer H L (1922) *Surg Gyn Obst* 34 241
- KRETSCHMER, H L *et al* (1934) Cancer of the bladder A study based on 902 epithelial tumors of the bladder in the carcinoma registry of the American Urological Association *J Urol* 31 423
- Kreutzmann H A R and Colloff B (1939) *Arch Surg*, 39 513
- Langham R F Thorp F and Hallman E T (1944) *Amer J Path* 20, 421
- McCown P E (1940) *J Urol* 43 533
- McDonald S and Sewell W T (1914) *J Path Bact* 18 306
- McDonald J R and Priestley J T (1943) *Surg Gyn Obst* 77 295
- Meeker L H and McCarthy J F (1923) *J Amer Med Assoc* 81, 104
- Nicholls M F (1933) *Brit J Surg*, 21 108
- Nieberle K and Cohrs P (1931) *Lehrbuch der Spec. Path Anat der Haustiere* Jena
- Nuboer J F (1925) *Virchows Arch* 254 70
- PATCH F S, and RHEA L J (1935) The genesis and development of Brunns nests and their relation to cystitis cystica cystitis glandularis and primary adenocarcinoma of the bladder *Canad Med Assoc J* 33 597
- Rehn L (1895) *Arch klin Chir* 50 588
- Renner M J (1931) *Surg Gyn Obst* 52 793
- Rousselot L M and Lamon J D (1930) *Surg Gyn Obst* 50 17
- Schlotthauer C F (1939) *J Amer Vet Med Assoc* 95 181
- Scholl A J (1924) *Surg Gyn Obst* 38 186
- Scholl A J (1944) *J Urol* 52 305
- Shaw W F (1923) *J Obst Gyn* 30 215
- Spieß P (1915) *Zbl allgem Path* 26 583
- Stalker L K and Schlotthauer C F (1936) *Amer J Cancer* 28 591
- Stewart R L (1926) *Brit J Surg* 13 667
- Stoerk O (1899) *Beitr path Anat* 26 367
- Stow B (1907) *Ann Surg* 46 233
- Venulet F (1909) *Virchows Arch* 196 73
- Willis R A (1941) *Med J Austral* 11 258
- Willis R A (1934) *The Spread of Tumours in the Human Body* p 92 London
- Wilson G H (1934) *J Path Bact* 39 171

not always be possible. The following is an example of a benign umbilical tumour probably of urachal origin.



FIG 226—Case VI Umbilical tumour probably of urachal origin ($\times 60$)

Case VI—For some years a woman of 38 had noticed a small mass beneath the skin at the border of the navel. This had enlarged recently and was excised. It was a well circumscribed loculated cystic mass 2.5 centimetres in diameter partly filled by friable papillary growth. Microscopically this consisted of thick folded layers of stratified epithelium devoid of spinous cells and cornification generally resembling the urinary transitional epithelium and traversed by fine connective tissue strands with blood vessels (Fig 226).

REFERENCES

- ABESHOUSE, B. S. (1943). Exstrophy of the bladder complicated by adenocarcinoma. *J Urol* 49 259 (A valuable review of carcinoma with exstrophy of vesical adenocarcinoma and of glandular metaplasia in the bladder).
- D'Aunoy R. and Zoeller A. (1930). *Arch Path* 9 17.
- Begg R. C. (1930). *J Anat* 64 170.
- Begg R. C. (1936). *Brit J Surg* 23 769.
- Bissell D. (1925). *Surg Gyn Obst* 40 323.
- Chisholm A. E. and Tudhope G. R. (1934). *Edinb Med J* 41 626.
- Culver H. and Forster N. K. (1923). *Surg Gyn Obst* 36 473.
- DAVIS, E. (1943). Chemical carcinogenesis: drugs, dyes, remedies and cosmetics with particular reference to bladder tumors. *J Urol* 49 14.
- Deming C. L. and Lindskog G. E. (1944). *J Urol* 52 309.
- Diehl K. (1925). *Virchows Arch* 256 666.
- Dolbey R. V. and Moore A. W. (1924). *Lancet* 1 587.
- Ewing J. (1940). *Neoplastic Diseases*. Philadelphia.
- Fairley N. H. (1931). *Brit Med J* 11 983.
- Feldman W. H. (1932). *Neoplasms of Domesticated Animals*. Philadelphia.
- FERGUSON, A. R. (1911). Associated bilharziasis and primary malignant disease of the urinary bladder with observations on a series of 40 cases. *J Path Bact* 16 76.

from vestigial or heterotopic tissues should not be admitted until it is certain that the normal tissues of the organ are incapable of producing such tumours, and (ii) 'embryonic rests' should not be invoked to avoid difficulties. Application of principle (i) will make us sceptical regarding the alleged Wolffian origin of serous cystadenomas, the alleged teratomatous origin of pseudomucinous cystadenomas, the alleged mesonephric origin of certain papillary growths, and a too facile identification of 'hypernephroma' of the ovary while application of principle (ii) will engender caution in interpreting Meyer's views on the origin of several of the special ovarian tumours from superfluous groups of "undifferentiated cells"

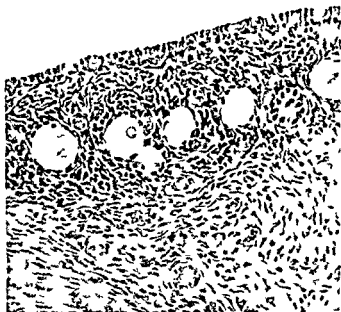


FIG. 227.—Ovarian cortex of an adult Australian phalanger *Trichosurus vulpecula* showing the cellular cortical blastema (stroma) and the germinal epithelium on the surface ($\times 250$)

(3) Distinction of ovarian from parovarian or tubal growths

This is not always possible. When a large tumour has involved both ovary and tube, and perhaps many other pelvic structures as well, its primary site may only be surmised, and for statistical or classificational purposes it is best excluded. It is noteworthy that the parovarium though a frequent source of cysts, very rarely gives origin to tumours, Nicholson (1923) recorded one example.

(4) The mistaking of secondary for primary growths

This is a frequent error. Bulky secondary growths in the ovary from small or silent growths elsewhere often simulate primary ovarian tumours and have caused many errors of diagnosis. The Krukenberg tumour now known to be always secondary usually to carcinoma of the stomach was regarded by Krukenberg as a primary ovarian growth. The ovarian metastases of silent alimentary

EPITHELIAL AND RELATED TUMOURS OF THE OVARY

OVARIAN tumours show great structural variety, the histogenesis of some of them is clear while of others it is still obscure. Several factors have combined to cause confusion in their classification and nomenclature namely (1) uncertainties as to the histogenetic relationships of some of the tissues of the normal ovary, (2) uncertainties as to the derivation of particular tumours from particular ovarian tissues (3) practical difficulties in some cases of distinguishing growths of ovarian origin from those of parovarian or tubal origin and (4) the frequent mistaking of secondary for primary growths in the ovaries. It will clarify subsequent description if these several sources of confusion are first discussed.

INTRODUCTORY REMARKS ON CLASSIFICATION

(1) The histogenesis of the tissues of the normal ovary

There is sufficient evidence both embryological and pathological for discarding the older view of Waldeyer that the follicular epithelium is derived from downgrowths from the 'germinal' epithelium on the surface and is therefore sharply distinct histogenetically from the surrounding ovarian stroma. It now appears clear that the so called 'stroma' of the cortex of the ovary is not a mere supporting tissue but an undifferentiated blastema from which both the epithelium of the follicles and the non epithelial thecal tissue arise. Examination of the primary follicles in young mammalian ovaries (Fig. 227) shows clearly that there is no structural distinction between those peri-ovular cells which will give rise to the stratum granulosum of the maturing follicle and those which will give rise to its theca interna, both of these arise by divergent differentiation from the indifferent blastema cells surrounding the ovum. The cortical stroma is thus *not* a mere connective tissue—it is the essential ovarian parenchyma and is distinct from the ordinary fibroblastic and vascular framework of the ovary. Further in the young active ovary, the so called 'germinal' epithelium on the surface is not everywhere sharply distinct from the subjacent cellular blastema, and it is probable that this epithelium also like that of the follicles is a product of, and closely allied to the labile subjacent cells. Unjustifiably sharp distinctions between germinal surface epithelium granulosa-cell epithelium and thecal tissues have come from too close a preoccupation with these several end products of differentiation. The essential tissue of the functional ovary is its peculiar cellular stroma: this is the plastic mother tissue from which the differentiated constituents of the organ are being constantly produced. This formative tissue then is sure to be of prime importance in the histogenesis of tumours.

(2) The histogenesis of particular tumours

Here two important principles pertinent for any region but especially so for the ovary need emphasis—(i) derivation of any tumour or class of tumours

of the normal adult ovary, of which the tumours appear to be but a neoplastic exaggeration. Papilliferous serous cysts of the ovary are clearly the same kind of growth, the cysts often having demonstrably arisen, as Shaw found, from the deeper parts of the surface crypts of the ovary. The once prevalent view that the intra ovarian papillary cystic growths were of Wolffian origin (see Ley) is certainly false, and it is noteworthy that, while cystic tumours of the ovaries are frequently papilliferous, parovarian cysts are very rarely so. The epithelium of the serous cysts and papillary growths closely resembles that of the surface of the ovary, and the fibrous connective tissue component corresponds

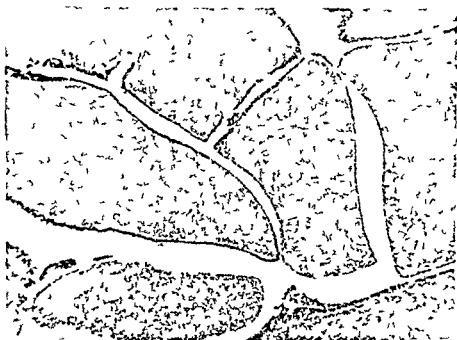


FIG. 228.—From an intracystic fibro papillary growth 15 centimetres in diameter in a woman of 64 ($\times 60$)

to the cortical ovarian stroma (Fig. 228). The tumours are mixed tumours, analogous to the mammary fibro adenomas, which they also resemble in showing varying relative proportions of epithelial and stromal tissues. Some tumours show predominance of epithelium and are appropriately called papillomas. Others show great masses of fibrous tissue clothed only on the outer surfaces by an epithelial layer—these have often been called 'fibromas'. However, all possible transitions between and combinations of, fibroma, papilloma, and papillary and simple serous cystadenoma occur, and the whole series clearly constitutes a single group.

The epithelium clothing the papillae varies from low cuboidal or flattened to tall columnar cells, and the latter sometimes show cilia and sometimes evidence of mucous secretion (Fig. 229). The fibromatous component in actively growing tumours is cellular and resembles cortical ovarian stroma, but in old, less active tumours it becomes densely fibrous and partly hyaline. Granular calcification is often present. As pointed out by Lepper a property common to these tumours is the secretion of serous fluid by the epithelium, the fluid accumulating

and other abdominal carcinomas may show glandular, papillary or cystic structure distinguishable with difficulty or not at all from primary ovarian carcinomas, and may easily be mistaken for such by the pathologist as well as by the clinician unless the mistake is corrected by careful necropsy. As shown by the many references which I have given elsewhere (1934 Chapters 12 and 23), mistakes of this kind have certainly caused great confusion in clinical and pathological records of ovarian cancer. My necropsy experience accords with that of Ley (1920) and others that secondary carcinoma in the ovary is commoner than primary carcinoma.

The foregoing sources of confusion not only render all mortality statistics regarding ovarian cancer valueless but also vitiate attempted analysis of the properties of ovarian tumours from many clinical series of cases as well. The mortality figures of ovarian tumours even were they based on accurate diagnoses, would still be useless for assessing the frequencies and properties of these tumours because many of the tumours are relatively benign and are cured by surgery. The only valid data for fruitful analysis are series of proved cases of specific kinds of tumours which have been identified by competent microscopical examination—an identification which in not a few cases can be regarded as fully verified only after careful necropsy.

We will discuss ovarian tumours under the following headings:

- (i) Benign fibro papillary growths and serous cystadenomas
- (ii) Pseudomucinous cystadenomas
- (iii) Malignant growths—carcinomas—corresponding to or arising from (i) and (ii)
- (iv) Brenner tumours
- (v) Granulosa theca and luteal tumours
- (vi) Arrhenoblastomas
- (vii) Dysgerminomas
- (viii) Sundry other tumours

This grouping is adopted for convenience and to include the currently accepted tumour types—it is not intended to be taken as a rigid classification into distinct species or to denote acceptance of the implications of all the names used. My own opinion regarding histogenesis is stated under each heading and is summarized at the end of the chapter and I recommend a paper by Robinson (1930) for sound views on this subject. Geist's book (1942) contains useful figures and references.

BENIGN FIBRO PAPILLARY GROWTHS AND SEROUS CYSTADENOMAS

(1) Incidence and causation

These are the commonest of ovarian tumours. Small surface or intra-cystic growths are often discovered incidentally at operation or necropsy. They occur in adult ovaries of all ages, are most frequent between 40 and 60 and may occur in old age. Nothing is known of their causation.

(2) Structure and origin

The structure of the warty or cauliflower like growths which spring from the surface of the ovary is essentially similar to that of the corrugations and crypts

been required over a period of many years. I recall a patient who had been tapped over 200 times, and Bland-Sutton recorded a patient on whom 299 tapplings were performed in 10 years. Spontaneous retrogression of disseminated peritoneal growths sometimes takes place, a subject well reviewed by Taylor and Alsop.

SIMPLE AND PAPILLARY PSEUDOMUCINOUS CYSTADENOMAS

(1) Incidence and causation

Pseudomucinous tumours are second only to the serous ones in frequency. They are unusual under the age of 30; most of them develop between 30 and 50, and they are rare again in old age. Nothing is known of their causation.

(2) Structure and origin

These tumours are too well known to require detailed description. Their usual multilocular structure, with large or small cysts within cysts, honeycomb areas, their mucinous contents varying in consistency from slightly slimy fluid to inspissated firm jelly or stringy tenacious material, to which old or recent haemorrhages or cholesterol deposits may add still greater variety, their lining of columnar mucus-secreting epithelium from which may spring papillary or convoluted intra-cystic growths, their thick outer cyst walls, and the huge sizes they may attain, are all familiar features.

Although most cystadenomas of the ovary fall readily either into this group or the previous serous group, some tumours are of borderline characters. Thus a unilocular cyst with all the appearances of a serous cystadenoma may yet contain slightly mucinous contents, or a multilocular tumour may show serous contents in some of the cavities and mucinous contents in others. These transitional types of cystadenoma are of significance in considering the origin of the pseudomucinous tumour. Three different opinions regarding this have been held: (a) that it represents overgrowth of a single component, usually considered to be alimentary, of a teratoma; (b) that it is related to the Brenner tumour (*see below*), and (c) that it is related to the serous cystadenoma, mucus secretion being acquired by metaplasia in the epithelium. I favour the third view, which however, does not exclude the second. The first view I regard as wholly speculative and devoid of any substantial basis. If it were true, we would surely see frequent examples of pseudomucinous tumours along with other obvious teratomatous tissues, but this is not the case. The occasional coexistence of teratoma and pseudomucinous tumour, of which I have myself studied examples, is too rare to be more than fortuitous. On careful search, the vast number of pseudomucinous tumours show no signs of teratomatous elements. Moreover, the alimentary and other mucus-secreting epithelia in teratomas do not resemble pseudomucinous cystadenomatous tissue; they are usually accompanied by muscle coats and often by lymphoid tissue, so that typical intestinal structure is reproduced. And does not ovarian pseudomucin differ chemically from alimentary or respiratory mucin? The fact that the pseudomucinous epithelium is unlike any normal component of the ovary is no argument for its teratomatous origin; metaplasia in tumours is frequent and no one suggests that mucoid carcinoma of the breast is teratomatous in origin. The rather frequent occurrence of tumours which

within the cystic growths or producing ascites from the surface ones. Scott has given a good account of a special sub group of the benign serous epithelial tumours which he has designated 'adeno fibromas', in which small glandular spaces are scattered through solid fibromatous tissue. These growths often show granular calcification and papillary characters in parts and they clearly represent only a particular type of the papillary cystic serous tumours.

The mode of origin of the tumours is of interest. Many of them clearly arise

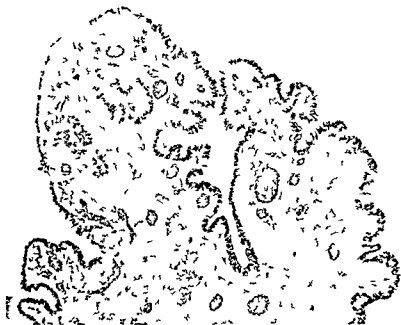


FIG. 229.—From pedunculated papillary growth in a unilocular ovarian cyst containing slightly mucinous watery fluid in a woman of 70 ($\times 60$)

over extensive fields of the ovarian surface and papillary tumours are often found springing simultaneously from the surface of the ovary and from the interior of one or several cysts in the ovary. Bilateral growths are frequent, and these are due to similar neoplastic change affecting both organs simultaneously or successively and not to metastasis from one to the other.

(3) Growth and behaviour

The tumours of this group grow slowly and non-invasively producing symptoms only by their bulk or by causing ascites. 'Benign' papillary tumours of this kind may yet disseminate in the peritoneum without showing any alteration of structure, the implant tumours showing the same benign appearance and non-invasive growth as the parent tumours. When this happens we must concede the appropriateness of now calling them carcinomas, yet they have not really altered in their characters. These growths thus show, like many others, that no sharp demarcation between innocence and malignancy is possible. Peritoneal dissemination of course increases the fluid output of the growths and every gynaecologist is familiar with cases of this kind in which frequent tapplings have

with (a) and (b) in the more malignant tumours, or may form the bulk of them (Fig 230)

(d) *Squamous cell structure*, due to metaplasia, has occasionally been found in cystadenocarcinomas, as in cases described by Nicholson and Rewell

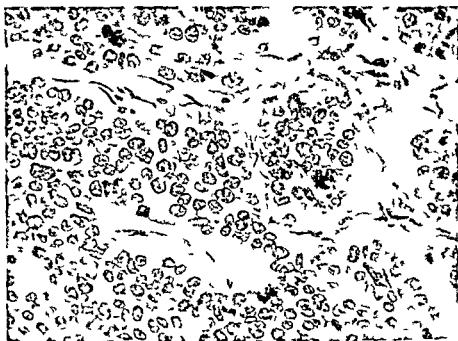


FIG 230—From an hepatic metastasis of a solid spheroidal-celled carcinoma of the ovary note mitotic figures ($\times 300$)

(3) Growth and behaviour

The tumours frequently become bilateral, grow to great sizes fill the pelvis, invade neighbouring viscera, cause intestinal obstruction or spread to the anterior abdominal wall. Peritoneal dissemination is frequent, leading to ascites, gelatinous accumulations widespread adhesions, or combinations of these. Transdiaphragmatic extension to the pleura and mediastinum is not unusual, and may cause the first signs of disease, as in Evans and Strachan's case. In surgical treatment of operable malignant ovarian tumours, Pemberton advised removal of the omentum as well as the uterus and both tubes and ovaries. Sampson's work leaves no doubt that fragments of ovarian carcinoma can implant themselves in the mucosa of the Fallopian tubes.

(a) *Metastases in lymph glands*

These are present in a high proportion of fatal cases, e.g. in 12 of my 17 necropsies. Ley recorded a decided difference between malignant pseudomucinous tumours and solid or papillary non mucinous tumours in this respect, no lymph nodal deposits were found in any of 9 cases of the former, while in the latter 12 of 16 cases showed affected lymph glands. The thoracic duct is occasionally affected. In a case described by Gibson and Findlay, the first symptom of disease was a large mass in the neck, presumably in lymph glands from which

combine mucinous and serous characters seem to me to point to their common origin from the ovarian epithelium. Careful study in serial sections of some very small pseudomucinous cysts is needed.

(3) Growth and behaviour

In their slow non invasive growth to large sizes, in the formation in some tumours of masses of papillomas, and in their usually favourable prognosis, pseudomucinous tumours resemble their serous counterparts. They differ from them in uncomplicated cases in not forming papillomas on the surface of the ovary and therefore in not causing secretory ascites. Rupture of the cyst walls by trauma or by the growth of prolific intra cystic papillomas however, leads to spilling of quantities of the mucinous secretion and of mucus secretory cells into the peritoneal cavity and to 'pseudomyxoma peritonei'. (See the original paper of Werth (1884) and other references by Willis, 1934.)

OVARIAN CARCINOMAS OF SEROUS OR PSEUDOMUCINOUS ALLIANCE

(1) Age incidence and causation

The mean age at death of my 17 necropsy cases of ovarian carcinoma was 59, and the youngest patient was 32. In Pemberton's clinical series of 149 cases the mean age was 49, 46 and 47 cases were in the fifth and sixth decades respectively i.e. a total of 61 per cent in the two decades, and the youngest patient was 26. I have seen a multilocular papillary cystadenocarcinoma, 20 centimetres in main diameter removed from a girl of 14. Pemberton's cases showed no significant peculiarities of menstrual history or fertility.

(2) Structure and origin

No sharp line of demarcation can be drawn between the more active papilliferous cystadenomas on the one hand and the invasive papillary cystic or solid carcinomas of the ovary on the other. All gradations of structure and behaviour are seen justifying the designation *cystadenocarcinoma* which has often been applied to such tumours. The development of invasive cancerous growth in part of an elsewhere benign serous or mucinous tumour is sometimes demonstrable. The carcinomas corresponding to or arising in the cystadenomas constitute the majority of malignant tumours of the ovary or the ovarian cancers of mortality statistics.

The varieties of structure seen in these carcinomas include the following:

(a) *Papillary adenocarcinoma* resembling or identical with the more active papillary growths in the cystadenomas or showing varying degrees of anaplasia is found in most ovarian carcinomas. Some of the papillary tumours of serous cystadenomatous origin show characteristic granular calcification—so called psammo-carcinomas (see Fig. 43).

(b) *Cystic mucoid adenocarcinoma* usually with papillary characters as well is a common type of growth and is the malignant variant of pseudomucinous cystadenoma.

(c) *Solid spheroidal celled or diffuse pleomorphic celled growth* is found mingled

cells first described by Walthard in 1903. These cell nests, which appear as small well defined yellowish nodules or tiny cysts on the surface of the ovary, tube or broad ligament, and which have not infrequently been mistaken for tubercles at operation, have a microscopic structure closely similar to that of the solid and cystic clumps of the Brenner tumours (Fig 231). Danforth drew attention to a peculiarity of the nuclei common to the cells of Brenner tumour and of Walthard nests, namely a distinctive median fold or groove giving the nucleus the appearance of a wheat grain.



FIG 231—A Walthard nest on the peritoneal surface of the Fallopian tube ($\times 120$)

The resemblance of Brenner tumours to the Walthard nests is indeed so close that it seems presumptuous to express any doubts regarding the now widely accepted origin of the one from the other. But it is necessary to point out that, while Walthard nests are more common in the serous coat of the tubes or broad ligament than in the ovaries, no extra ovarian Brenner tumours have been reported. Moreover, unreserved acceptance of the Walthard nests as the origin of Brenner tumours raises fresh difficulties as to the origin of the cystadenomas, since there seems to be no doubt (i) that Brenner tumours are related histogenetically to pseudomucinous tumours (ii) that pseudomucinous and serous cystadenomas are not sharply separable, and (iii) that serous cystadenomas and fibro papillomas arise from the surface epithelium of the ovary. However, the great diversity of structure in the cell groups found in or near the ovaries affords an explanation of these relationships. These include nests of granulosa like cells or of columnar, ciliated or goblet cells, or of stratified squamous like epithelium like that of the Brenner tumours, and they serve to show the variety of structural differentiation of which the gonadal and juxta gonadal tissues are capable. If this is recognized, then tumours showing combinations of cystadenomatous and Brenner structure will cease to surprise us and we will be prepared to readmit Brenner's original view that tumours of this kind may arise also from the ovarian follicles.

the tumours had invaded the subclavian vein and superior vena cava and projected into the right atrium

(b) Blood borne metastases

These are relatively infrequent, they were present in only 4 of my 17 necropsies. The lungs and liver are the usual sites but other viscera and bones are affected occasionally (Bankart Erdheim). Nicholson (1909) saw multiple pulmonary metastases from a well differentiated pseudomucinous growth.

BRENNER TUMOURS

(1) Incidence

In 1907 Brenner described 3 cases of the tumour which now bears his name he believed it to arise from the epithelium of the follicles and accordingly named it 'oophoroma folliculare'. In 1932, Meyer recorded 22 cases and distinguished the tumour sharply from the granulosa cell tumour. In 1935 62 cases had been reported (Bland and Goldstein). In 1939, 122 cases (Novak and Jones), and in 1942 170 cases (Fox).

The age distribution of the tumours in successive decades was shown by Fox's review to be as follows

Decade - -	1	2	3	4	5	6	7	8	Total
Number of cases -	0	1	11	26	41	47	27	5	158

The tumours have been bilateral in 8 per cent of the cases, 3 of Fox's 4 cases had bilateral tumours.

(2) Structure and origin

(a) Gross appearance

Huge tumours of 18 and 15 pounds have been seen but most tumours are of small or moderate size. They may be wholly solid or may show a solid mass of growth in the wall of a cyst usually a pseudomucinous cystadenoma as in the cases of Hicks and of Marwil and Beaver. The tumour tissue is firm and fibrous in texture and often has a distinctly yellowish colour.

(b) Microscopic appearance

Well defined rounded nests or trabeculae of large polyhedral epithelial cells are set in a plentiful dense fibrous stroma. The nests may be solid or may contain small rounded well defined cavities and the epithelium often appears stratified. The cells lining the small cystic spaces sometimes assume the typical form of columnar mucus secreting epithelium and in different cases, all transitions between typical Brenner epithelial nests and pseudomucinous cystadenomatous structure are seen.

(c) Origin

Brenner's suggestion that his tumour arose from the epithelium of the ovarian follicles has been widely displaced by Meyer's view that it arises from nests of

luteal cells, it is equally certain that granulosa cells also become luteal cells. Case III below showed very clearly the luteinization of groups of granulosa cells. In view of the origin of granulosa epithelium from undifferentiated ovarian stroma, it is not surprising that luteinization may affect either of these and the controversy as to whether luteal cells come mainly from "epithelial" or "non-epithelial" precursors loses interest.

This view of the relationships and maturational changes in this series of tumours is now adopted by most informed writers on the subject, e.g. Traut and Butterworth Harvey *et al* and Bettinger *et al*. Other noteworthy contributions include Löffler and Priesel's account of 6 theca cell tumours showing transitions from plump lipid rich cells to fibrous tissue, Novak and Long's outline of ovarian tumours with hormonal effects, and Furth and Butterworth's study of granulosa cell and other tumours in the ovaries of irradiated mice. Under the apt heading 'Life Cycle of Graafian follicle like Tumors', Traut and Marchetti pointed out the wide variation in degree of maturation in the different parts of granulosa cell and theca cell tumours. "The result of periodic growth is that the neoplasm is frequently an aggregate of groups of cell masses produced at different times and having different degrees of maturity and senescence". The hormonal effects of the tumours vary according to the total amount of functionally active tissue at any given time.

(2) Age incidence, site, causation

A few oestrogenic tumours have occurred in young people, even before puberty. Probably the youngest subject with a tumour of this type was Southam's patient of 2 years and 10 months in whom vaginal bleeding, enlarged breasts and the growth of pubic hair were relieved by removal of an ovarian tumour said to be a 'round celled sarcoma'. Bland and Goldstein reported a granulosa cell tumour in a child of 7 with precocious menstruation, which was relieved by removal of the tumour but later recurred when a second tumour developed in the opposite ovary. However, only about 10 per cent of granulosa cell tumours appear under the age of 20, and about 50 per cent of them appear after the menopause. Theca cell tumours are rather later to appear than granulosa cell tumours—only about 10 per cent of these appear before the menopause. The patients' ages in the 8 cases I have studied were

Predominantly granulosa cell tumours	-	-	-	10	39	46	56	66
Predominantly theca cell tumours	-	-	-	57	72			
Tumour with granulosa and theca cells in nearly equal proportions	-	-	-	-	52			

Granulosa cell tumours are bilateral in only a small proportion, about 10 per cent of cases. Theca cell tumours are rarely bilateral. Extra ovarian granulosa cell or theca cell tumours have been described in the broad ligament e.g. by Ragins and Frankel and by Powell and Black and I have examined one specimen of this kind given to me by Dr H. Bettinger, a typical granulosa cell tumour of trabecular pattern weighing 800 grammes, from a woman aged 56 (Fig 232).

Nothing is known of the causation of these tumours, but Furth and Butterworth's experimental production of them in mice by means of X rays is of great interest.

(3) Growth and behaviour

Brenner tumours grow slowly are well circumscribed and are cured by surgical removal. Recurrence and metastasis have not been reported, and there is no evidence that any of the carcinomas of the ovary are malignant variants of the Brenner tumour. However, slightly augmented growth and slight anaplasia might readily disguise a tumour of Brenner type and lead to its inclusion amongst the solid or cystic carcinomas of the ovary, without more specific recognition. Brenner tumours are usually unaccompanied by hormonal disturbances, but in Marwil and Beaver's case a structurally typical Brenner tumour was associated with endometrial hyperplasia and haemorrhage in a woman of 77. Bettinger reported the coexistence of uterine carcinoma and myomas with a Brenner tumour and a pseudomucinous cyst.

GRANULOSA CELL, THECA CELL AND LUTEAL TUMOURS

(1) Introductory

The term granulosa cell tumour was originally applied to various solid epithelial tumours solely on micro structural grounds e.g. by Werdt (1914) Lepper *et al* (1932), and many others. But as it became recognized that some of these growths produced oestrogenic hormone, it became customary to restrict the name to tumours accompanied by signs of hyperoestrinism. This restriction of the term however, introduced two difficulties: on the one hand there occurred tumours structurally of granulosa cell type, yet without obvious hormonal effects, and on the other hand there were some tumours with such effects but of non-epithelial structure.

The first difficulty is not a serious one, in all groups of endocrine tumours we encounter some usually the less well differentiated members of the class, which are without demonstrable endocrine effects. We shall then admit as granulosa cell tumours any which are structurally characteristic even though they are devoid of functional results.

The second difficulty, that of distinguishing between granulosa-cell and theca cell tumours is resolved by recognizing the histogenetic relationship between granulosa and theca cells in the ovary as outlined at the opening of this chapter. Just as the granulosa and theca cells of the ovarian follicles are products of divergent differentiation of a common mother tissue the undifferentiated ovarian blastema so granulosa-cell and theca-cell tumour tissue are closely akin and are indeed often present together in a single tumour (Traut and Marchetti, Dockerty, Henderson). All the tumours of this group are fundamentally tumours of the formative ovarian stroma: epithelial and thecal differentiation in them proceeding in varying proportions and to varying degrees. Moreover the tumour tissue undergoes maturation changes comparable with those of normal follicles namely luteinization and band like fibrosis and hyaline change. Luteal-cell tumours are thus allied to or but variants of granulosa-cell and theca-cell tumours and no doubt dense fibromas of the ovary are the end product of tumours of this series just as the corpus fibrosum is the end product of the ovarian follicle. The cell transitions observed in the tumours are of interest as regards the still debated origin of luteal cells—whether from the granulosa epithelium or from the thecal stroma. While it appears certain that stroma cells can differentiate directly into

Epithelial granulosa cell structure—Some growths show a well differentiated folliculoid pattern, at once recalling that of the normal stratum granulosum and showing Call Exner bodies or conspicuous rosettes (Figs 233, 234), it was this type which von Kahliden originally described in 1895 as "Graafian follicle

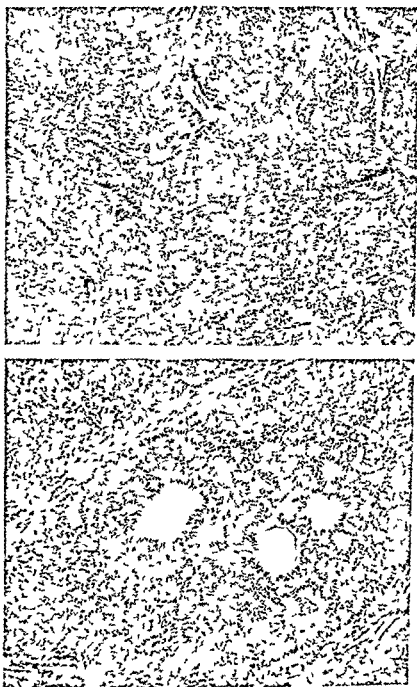


FIG 233 —From a granulosa-cell tumour of the ovary in a woman of 66 showing many Call Exner rosettes and small cysts ($\times 100$)

adenoma'. Or the epithelium, though still composed of typical granulosa cells, may form irregular trabeculae or coarse or fine networks (Fig 235), or the

(3) Structure

(a) Gross appearance

Granulosa cell tumours are well circumscribed usually stoutly encapsulated growths, consisting of firm white or patchily yellow solid tissue which, however, may contain small or large cystic spaces. Hormonal results lead to the removal of some of the tumours while still small, but in many other cases the growths



FIG. 232.—From a huge granulosa-cell tumour of the broad ligament in a woman of 56 ($\times 120$)

have attained large sizes. The specimen removed from a Nigerian woman by Kelsey weighing 20 pounds, is probably the largest recorded. Most theca cell tumours are wholly solid, consisting of firm fasciculated tissue resembling fibrous tissue but often with a distinct yellow colour. However some of these growths contain cysts and one of my specimens a large tumour from a woman of 57 consisted of a single cavity surrounded by a wall of tumour tissue measuring up to 3 centimetres thick.

(b) Microscopic structure

This is well described and depicted by the writers already cited and is shown also in Figs 232–238. It is important to recognize that epithelial and stromal tissues often coexist in one tumour that one tumour may show great diversity of structure from part to part and that all gradations may be seen between the several types of structure. However most tumours do consist predominantly of one or another type of tissue so that the names 'granulosa-cell tumour', 'theca-cell tumour' and 'luteal-cell tumour' have descriptive value.

ovarian stroma, or they may be indistinguishable from fibrocytes, forming interlacing fasciculi with plentiful intercellular collagen fibres. In the more cellular areas the cells usually contain plentiful doubly refracting lipid droplets which stain characteristically with fat stains. Lipoid rich parts of the tumours have a distinct yellow colour on section. In the more fibrous areas intra-cellular lipoid material is more scanty. Cellular and fibrous areas may alternate, and banded fibrous and hyaline zones may recall the appearance of corpora fibrosa at different stages (Fig 236). There is no doubt that many, if not all, fibromas of the ovary are really fibrous theca cell tumours.



FIG 236—From a theca-cell tumour 10 centimetres in diameter from a woman of 22 (Case II of Buttinger *et al*), showing fibrous patches like corpora albicantia in the cellular growth ($\times 120$)

Luteal cell structure—This is frequent in parts of granulosa cell or theca-cell tumours and is sometimes predominant, giving the tumour a bright yellow colour like a giant corpus luteum (Henderson). Geist *et al* and Traut *et al* have given useful accounts of luteinization in these tumours.

(4) Origin

In the preceding discussion it has been implied that the granulosa and theca cell tumours arise from the normal follicular tissues or from the formative bipotential ovarian stroma. There is no need to suppose with Meyer and with Novak (1941) that these growths are "embryonic" or "dysontogenetic" and that they cannot arise from normal ovarian structures. Furth and Butterworth's experiments

epithelial cells may be scattered rather diffusely amidst accompanying undifferentiated stroma (Fig 238)

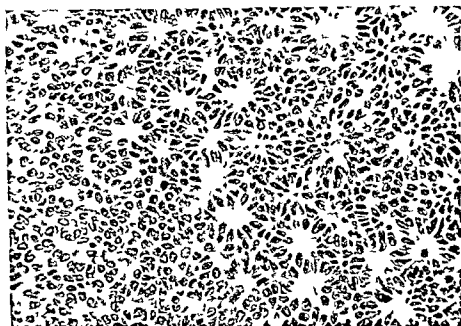


FIG 234—Detail of the rosettes of Fig 233 ($\times 300$)

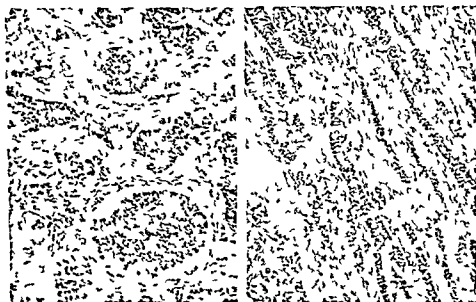


FIG 235—From a granulosa-cell tumour 10 centimetres in diameter weighing 400 grammes from a woman of 46 ($\times 100$)

Theca cell structure—This shows spindle cells arranged in groups or bundles. The cells may be plump and closely packed resembling those of undifferentiated

solid and partly cystic with a thick fibrous capsule. The other ovary appeared normal. After removal of the tumour the uterine haemorrhages ceased. *Histology*—Small and large cystic spaces were lined by irregular thick layers of epithelium of granulosa-cell type and solid areas consisted of masses and trabeculae of similar epithelium containing small cysts (Fig 237). There was much intervening stroma consisting of poorly cellular soft fibrous tissue.

Case II—A married woman aged 39 had had amenorrhoea for 3 years followed by recent return of menstruation and had noticed a lower abdominal tumour for some months. At operation a large right ovarian tumour without adhesions was removed. The left ovary and uterus appeared normal. The tumour was smoothly ovoid with a thick fibrous capsule and weighed 900 grammes. On section its tissue was pink grey finely spongy with many tiny and some larger cystic spaces. *Histology*—Typical granulosa cell tumour mainly of trabecular and folliculoid structure with cystic spaces.

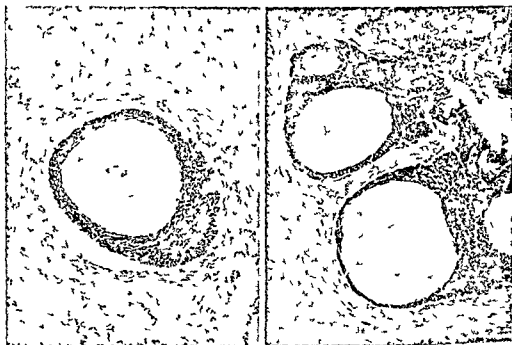


FIG 237—*Case I* Cystic granulosa cell clumps ($\times 80$)

Case III—A married woman aged 52 mother of 3 children the eldest 25 and the youngest 18 gave the following unusual menstrual history. Menses commenced when she was 18 years old occurred regularly every 4 or 5 weeks but were copious and lasted 10 to 14 days. During the previous 12 months they had occurred every 6 or 7 weeks but lasted about the same time as previously. For 3 months abdominal enlargement had been noticed and examination showed uterine prolapse and signs of a large ovarian tumour. This was removed along with the enlarged uterus. The tumour comprised a large cyst containing clear serous fluid and with a slightly granular or papillary lining and at one side a well defined mass of solid growth 3.5 centimetres thick with a fibrous cut surface and a distinct yellow colour. The endometrium measured up to 1 centimetre thick. *Histology* (Fig 238)—The solid part of the growth consisted of mingled cellular and fibrous stromal tissue with however many scattered patches of well differentiated granulosa cells including many luteal cells. The latter were clearly luteinized granulosa cells all transitions from the one to the other were seen. All transitions were seen also between cellular stroma and epithelial cells. The tumour was thus an excellent example of mixed stroma-cell granulosa cell and luteal-cell structure.

afforded good evidence that granulosa cell tumours in mice do indeed arise from the granulosa epithelium of the ovarian follicles and that this tissue is not, as has often been asserted a satellite tissue entirely dependent for its existence on the presence of ova. Proliferation of follicular epithelial and interfollicular spindle shaped cells both of which are probably derivations of the germinal epithelium give rise to granulosa cell tumors. These tumors may be composed of spindle shaped cells like those of the ovarian stroma or of epithelial cells like those of ovarian follicles or of luteinized epithelial cells, or of several different morphological variants of the granulosa cells. In brief in accordance with the principle enunciated earlier in this chapter we can interpret the structure and relationships of the tissues in these tumours in terms of the normal structure and functions of ovarian tissue, without resort to hypothetical origins from rests or superfluous groups of undifferentiated cells. Probably however, granulosa cell rests are not exempt from neoplasia, extra ovarian granulosa cell tumours may arise from such heterotopic cell groups.

(5) Endocrine effects

As described in the papers of King and of Meyer Novak and Long Traut and Marchetti and others, the most characteristic endocrine result of functional granulosa cell and theca cell tumours is cystic endometrial hyperplasia sometimes as in the case described by Arnold *et al*, with decidual change in the hyperplastic endometrium. Occurring before puberty, precocious sexual development and menstruation are induced, occurring in adults before the menopause the result is either menorrhagia or amenorrhoea followed by irregular bleeding occurring after the menopause irregular severe uterine haemorrhage results. Many of Furth and Butterworth's mice with granulosa cell tumours showed endometrial hyperplasia. Mammary enlargement and secretion have been recorded in a few cases.

Uterine abnormalities other than endometrial overgrowth have frequently been noted in association with these ovarian tumours. King's cases showed multiple myomas and adenomyosis. Of Henderson's 21 cases of granulosa-cell tumour 5 had uterine fibroids and 2 had carcinoma of the endometrium while of 9 cases with theca-cell tumours, 5 had fibroids and 3 had endometrial carcinoma. Thus of the total 30 cases 10 had fibroids and 5 had carcinoma—proportions too great to be fortuitous suggesting that the prolonged oestrinization was indeed a factor in causing the uterine tumours. Stohr reported 3 cases of well differentiated folliculoid granulosa-cell tumours with accompanying endometrial hyperplasia and supervening carcinoma. Furth and Butterworth saw an excessive number of mammary tumours in their mice with experimentally produced ovarian tumours. A fruitful research would be to study the follow up history of all cases of granulosa-cell and theca-cell (and other) tumours of the ovaries for possible subsequent lesions of the uterus or breasts (see Case IV below). Whether luteinized ovarian growths produce excessive progesterin has not yet been determined.

The following 4 of my cases were noteworthy because of their hormonal disturbances

Case I—A child aged 10 had menstruated irregularly for some months and was found to have a lower abdominal tumour. Laparotomy disclosed a large ovarian growth partly

(6) Malignancy and metastasis

With few exceptions, tumours of both granulosa-cell and theca cell types are relatively benign, in most series recurrence or metastasis has been infrequent. Novak and Brawer, however, reported clinical malignancy, either extension to peritoneum or recurrence, in 9 of 36 cases of granulosa cell tumour, and Traut and Marchetti found clinical or histological evidence of malignancy in 8 of 54 tumours studied. But it must be recognized that disorderly or diffuse structure in these growths does not imply clinical malignancy and that a false histological diagnosis of malignancy may easily be made. In Henderson's series of 30 cases, only 1 granulosa cell tumour recurred, and none of his 9 thecomas was malignant. In none of my 8 cases was recurrence or metastasis reported.



FIG. 239—Case IV. Cystic endometrial hyperplasia accompanying theca-cell tumour in a woman of 72 ($\times 4$).

In the remarkable case described by Arnold *et al*, the patient died of recurrent growth at the age of 63, 20 years after removal of the primary ovarian tumour, and metastases were present in the peritoneum, liver, vertebrae, ribs and many lymph glands.

TUMOURS ACCOMPANIED BY MASCULINIZATION ARRHENOBLASTOMAS

(1) Introduction

The name "arrhenoblastoma" was applied by Meyer in 1930 to rare ovarian tumours accompanied by signs of masculinization, including amenorrhoea, sterility, atrophy of the breasts and uterus, enlargement of the clitoris, and

Case IV (Dr F G C de Crespigny's case)—A married woman aged 72 complained of irregular uterine haemorrhage for the last 8 years. Radical removal of the left breast for carcinoma had been performed 7 years ago. Operation revealed a large right ovarian tumour which was removed along with the enlarged uterus. The tumour was mainly

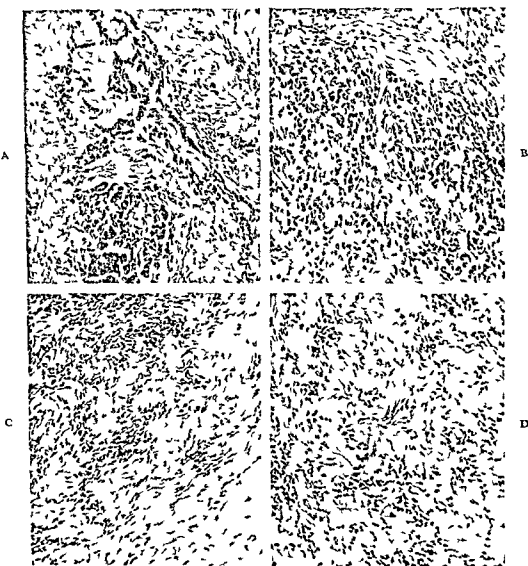


FIG. 238.—*Case III*. A = clumps and tendrils of granulosa-cells. B = partially luteinized area of granulosa cells. C = theca-cell structure. D = trabecular hyaline fibrosis in a theca-cell area of the growth ($\times 100$).

solid but partly cystic and measured 20 centimetres in diameter. The uterus showed great thickening of both the endometrium and myometrium. *Histology*.—Predominantly theca-cell tumour with alternating areas of poorly cellular fibrous tissue and undifferentiated cellular spindle-celled stroma but containing also groups of polyhedral epithelium like cells. The endometrium measured up to 1.5 centimetres thick and showed extreme cystic hyperplasia (Fig. 239).

structures closely like those of granulosa cell tumours. Muchler and Black reported a case and reviewed other records of "gynandroblastomas", i.e. tumours accompanied by masculinization but with continuation of menstrual bleeding and other signs of hyper oestrogenism. Microscopically these tumours have shown no constant structural pattern, they have been regarded as combinations of granulosa cell tumour and arrhenoblastoma", and lipoid laden cells in them, as in the arrhenoblastomas', have been regarded as Leydig cells



FIG. 240—Case VI Arrhenoblastoma. A shows slight and B pronounced luteal change in the epithelial masses ($\times 100$)

Some tumours have contained glandular structures lined by columnar mucous epithelial cells.

Kanter and Klawans described masculinization in a woman of 33, with a huge cystic ovarian tumour evidently of teratomatous nature, containing

hairiness Although it has often been assumed largely because of the name, that these tumours must arise from testicular elements in the ovary, this is doubtful and their precise histogenesis is uncertain (*see below*) The best reviews are those of Buttner (1932) and Norris (1938) Most of the tumours have appeared before the menopause the age extremes of the few reported cases are 16 and 66 They are almost always unilateral Nothing is known of their causation

(2) Structure

There is nothing distinctive about the gross appearance of the tumours
 ✓ They may be large or small wholly solid or partly cystic white or yellow

Microscopically also, the structure is usually non distinctive and variable Some of the growths have consisted wholly or in part of tubular glandular tissue Meyer and others say that this resembles that of Pick's 'adenoma tubulare' of the atrophic cryptorchid testis, the structure of which is similar to that of tubular adenomas of the ovary unaccompanied by hormonal disturbances (Heesch) But most 'arrhenoblastomas' show no microscopical characters sufficiently distinctive to relate them to any special structures consisting of solid carcinoma-like epithelial trabeculae and masses with or without suggestions of glandular structure or of diffuse growth devoid of recognizable epithelial characters or of all of these Boltuch depicted regimented cell groups Mucoid ✓ glandular acini have been described in several tumours I have studied two specimens of 'arrhenoblastoma'

Case V (Dr C S Fitzpatrick's case)—A married woman of 32 complained of sterility Her menses had been normal until 2½ years earlier when complete amenorrhoea developed This was unrelieved by intensive oestrin treatment Distinct features of masculinization included hypertrophy of the clitoris and atrophy of the breasts Laparotomy disclosed a small well defined rounded tumour 2 centimetres in diameter in the right ovary which was removed On section the tumour consisted of greyish pink solid tissue Microscopically this showed well-defined anastomosing solid epithelial cords with some tiny cystic spaces but no definitely glandular lumina The structure closely resembled that of the trabecular variety of granulosa-cell tumour

Case VI (reported by Dr H A McIntyre 1942)—A solid yellowish right sided ovarian tumour was removed from a woman of 26 who had developed marked hairiness and an enlarged clitoris *Histology* (Fig 240)—The tumour was a mixture of epithelial cords and diffusely cellular tissue The cords consisted mainly of closely packed small polyhedral cells, with however many groups of larger vacuolated cells like foam cells resembling the luteinized cells of granulosa-cell tumours Between the epithelial trabeculae lay diffusely cellular growth consisting of polyhedral and irregular cells otherwise resembling those of the trabeculae At one part of the periphery lay an area of uniform spindle-celled growth devoid of epithelial characters and structurally resembling theca-cell tumour

(3) Nature and origin

In both of the foregoing cases, the microscopic resemblance of the tumours
 ✓ to granulosa-cell tumours and the presence in one of them of both theca-cell like and lutein-cell like structures raise the question of the possible relationship of these tumours to those of the Graafian follicle group In other reported cases also the tumour structure and the hormonal effects have raised the same question Thus in Mäckenrodt's case No 14 (tabulated by Büttner) the tumour was recorded as granulosa-cell like in parts and Benecke depicted folliculoid

Yet many permanent cures have been obtained by removal of the tumours in the early stages. In Norris's case a small primary tumour produced widespread metastases in the liver, lungs, mediastinum, kidney, adrenal and opposite ovary.

SEMINOMA LIKE TUMOUR OF THE OVARY 'DYSGERMINOMA

The name dysgerminoma was applied by Meyer to solid carcinomatous ovarian tumours with a microscopic structure resembling that of seminoma of the testis and devoid of endocrine effects. Indeed French pathologists had previously called these tumours ovarian "seminomas" and had supposed them to arise from testicular elements in the hilum of the ovary. Meyer, however, assumed their origin (and also the origin of seminomas of the testis) to be from undifferentiated germinal cells of indeterminate type. Werdt's case VI, classified by him as a granulosa cell tumour, was clearly one of dysgerminoma. The best reviews of the subject are those of Seegar and of Sailer which cover over 100 cases.

(1) Age, site, causation

(a) Age

About three quarters of the subjects are under 30 years of age, and about one half of them under 20. Young children however, are not affected, the youngest recorded case being 9 years old.

(b) Site

The right ovary is more often affected than the left. Seegar's review showed right sided growths in 48 per cent, left sided in 26, and bilateral growths in 26 per cent of cases. and Sailer's 5 cases had 4 right sided tumours and 1 left sided. Following removal of a unilateral tumour, the risk of development of a second tumour in the remaining ovary is slight, this has been recorded only occasionally, e.g. by Potter. In 6 recorded cases, following removal of one affected ovary the patient has had a subsequent fruitful pregnancy.

(c) Hermaphroditism or pseudo hermaphroditism

This has been present in a singularly high proportion of cases. Meyer's original review comprised 27 tumours associated with and 21 without pseudo hermaphroditism, and he stressed that dysgerminoma is the commonest tumour of the gonads in pseudo hermaphrodites. The frequency of the association was probably over estimated by Meyer, because the interest excited by it led to its being frequently recorded, the proportion of subsequently reported cases of dysgerminoma with associated pseudo hermaphroditism has been much lower. Dysgerminoma in pseudo hermaphrodites occurs at rather later ages than in other subjects. pseudo hermaphrodites have provided a large proportion of the tumours over the age of 30. A positive Aschheim Zondek or Friedman test has been observed in a few patients with dysgerminoma (Potter).

(2) Structure and origin

The tumours are usually well defined completely solid composed of firm homogeneous white tissue, degenerative or cystic changes are usually not prominent. Large sizes have often been attained before operative removal, in

in addition to embryonic rete and 'arrhenoblastoma' tissue, glandular cysts and cartilage (How could embryonic rete and 'arrhenoblastoma' tissue be identified in a teratoma?) Mechler and Black also suggested that "gynandroblastomas" may be teratomatous. To add to the confusion regarding the nature and origin of masculinizing tumours of the ovary we must also admit the possibility of adrenal cortical tumours occurring in this organ since accessory nodule of adrenal cortex are sometimes present in the peritoneal tissues near the ovary (see below). The tumour described by Jolles and Gleave (1945) as arrhenoblastoma in an hermaphrodite woman of 61 has no claim to that title there was no evidence that it had androgenic activity.

In an important paper Burrows (1943) warns that it is a gross mistake to suppose that because a tumour produces androgen it therefore should have an architecture like that of the testicle. In the male, androgens are derived from the interstitial glandular cells of the testicle which have no tubular or strand like arrangement. The structure of 'arrhenoblastomas' is unlike that of interstitial cell tumours of the testis. Again, 'Some ovarian tumours which induce hirsuties and other masculine phenomena are the colour of corpora lutea and are composed of cells which resemble those of luteal tissue others might be described from their cytological appearance as thecomas or as granulosa cell tumours and yet others look like tumours derived from adrenal tissue. In fact by examining sections of an ovarian tumour under the microscope no reliable guidance can be obtained either from their anatomical arrangement or individual appearance as to the nature of the hormones if any which the cells may have produced. Burrows concludes 'Criticism is made of the terms arrhenoblastoma and granulosa cell tumour and it is suggested that they might be discarded. It is proposed that the term arrhenoma might be used to denote androgen producing tumours and theeloma to denote those which produce oestrogen irrespective of the location of the tumours in the body or of their histological appearance'.

I agree with Burrows that the name 'arrhenoblastoma' has conveyed a false implication of origin from male gonadal tissue and that the androgen producing tumours of the ovary to which it is applied are of undetermined and possibly of diverse nature. But I think the terms granulosa-cell and theca cell tumour can legitimately be used to designate tumours which clearly correspond to these elements or their precursors in the normal ovary, and which often though of course not always produce the appropriate hormone. The histogenesis of the oestrinizing tumours is I think well established that of the androgen producing tumours is still uncertain. It would not be surprising if further research should show that the two classes of tumours are really one and are both derived from the ovarian parenchyma. Oestrogens and androgens are closely kindred substances and are readily interconvertible both in the body and *in vitro* (Burrows 1945). Androgenic activity of an ovarian tumour may well be the result of disturbed chemistry in a primarily oestrogenic tissue.

(4) Growth and metastasis

The androgen producing tumours of the ovary appear to be rather more malignant than the oestrogen producing granulosa-cell and theca-cell tumours.

Patient remained well until April 1943 when she began to suffer from attacks of abdominal pain which were thought to be due to recurrent growth and which improved following deep X ray treatment. In April 1944 skiagrams showed large rounded shadows in the right lung field. deep X ray irradiation was followed by marked diminution of these. In October however right sided pleural effusion had developed and multiple swellings had appeared on the chest and skull the largest 3 centimetres in diameter. X ray irradiation of these also led to their reduction. The patient died in December 1944 at the age of 22. *Necropsy* showed many partly white and partly yellow and degenerated metastatic growths in many abdominal thoracic and cervical lymph glands in the lungs liver both adrenals subcutaneous tissues skull ribs and pelvic peritoneum. From the pelvic deposits the uterus was extensively invaded from the lumbar lymph nodal deposits the right kidney was invaded and from the massive thoracic lymph nodal deposits the growth had invaded the 6th and 7th dorsal vertebrae and compressed the spinal cord causing paraplegia.



FIG 241 —Case VIII Dysgerminoma from a metastasis in lung ($\times 120$)

The left ovary was intact and rather small. *Histology*—In all situations the tumours had a similar structure more cellular than that of the primary growth with less plentiful stroma and with many mitotic figures (Fig 241).

SUNDRY OTHER TUMOURS

To conclude the list of epithelial tumours of the ovaries the following remain for consideration

(1) Epithelial tumours of teratomatous origin

Otherwise benign teratomas of the ovary occasionally give rise to squamous cell carcinoma argentaffin carcinoma or other growths of a single tissue component. These are described in Chapter 61, where also the relationship of thyroid tumours (ovarian 'strumas') to teratomas is discussed.

my two cases described below the tumours weighed 1,900 grammes and 3 350 grammes respectively

Seminoma like ' summarizes the microscopical appearances of the tumours which consist of well defined or ill defined groups or columns of large rounded epithelial cells set in a connective tissue framework of variable amount and density, accompanied by a variable number of lymphocytes (Fig 241)

The histogenesis remains obscure The favourite view is Meyer's that the tumours arise from 'indifferent germ cells'—whatever that may mean The early age incidence, the significantly frequent association with pseudo hermaphroditism, and the preference for the right ovary certainly suggest a relationship to some developmental disturbance Whether the tumours are indeed seminomas derived from persistent male tissue in an indifferent bisexual gonad is uncertain but I think, not improbable Against this view it has been argued that the dysgerminomas are more benign in behaviour than testicular seminomas but this argument is of little weight, for the growth of seminoma in the female might well progress very differently from seminoma in the male because of endocrine differences between the two sexes It is noteworthy here that seminomas of the testis in dogs though clearly the counterparts of those in human beings are relatively benign However, too much stress must not be placed on the close histological resemblance of dysgerminoma to testicular seminoma for other tumours also sometimes mimic seminoma in appearance e.g. some pineal and pituitary tumours (q.v.)

(3) Growth and metastasis

Though more tardy and less aggressive in growth than testicular seminomas and sometimes cured by surgical removal the seminoma like tumours of the ovary are essentially malignant and capable of metastasis Klasten referred to the recorded instances of metastases in lymph glands and peritoneum and described a case in which the first sign of disease was the appearance of a large lymph nodal metastasis in the neck In Kirschbaum and Newman's case, necropsy 3 years after removal of the ovarian growth showed many deposits in the lungs liver kidneys and peritoneum

The following two personally studied cases exemplify the two opposite terminations of the disease—cure of a large tumour by excision and extensive dissemination The second case also illustrates the radio sensitivity of the tumour

Case I II—History—An otherwise healthy nurse aged 21 had noticed an abdominal mass for several weeks and laparotomy revealed a smooth surfaced irregularly ovoid left ovarian tumour which was easily removed This weighed 1 900 grammes measured $21 \times 12 \times 12$ centimetres, and consisted of uniform firm white growth devoid of any pattern and without cysts The patient remained in good health over 6 years later *Histology*—Large spheroidal-cell carcinoma of typical seminoma like appearance with masses and columns of large polyhedral cells set in a moderately abundant fibrous stroma containing a few lymphocytes

Case I III—History—In August 1940 a girl aged 18 had noticed abdominal discomfort and enlargement for 2 months and a diagnosis of fibroid was made Laparotomy however revealed a large solid irregularly ovoid tumour of the right ovary which was removed This weighed 3 350 grammes (over 7 pounds) and consisted of uniform firm white growth without cysts *Histology*—Seminoma like growth generally resembling that of the previous case but with more lymphocytes in the stroma *Subsequent progress*—

serous cystadenoma, his Figures 15 and 20 strongly suggest ovarian parenchymatous tumours of the usual kinds, while in his Cases IX and X the "mesonephroma" tissue was a component of teratomas. The figures accompanying the description of Kazancigil *et al.* of 3 cases of "papillo endothelioma" show clear epithelial structures and in their Case I they recorded that granulosa and follicle like structures were 'included' in the tumour. Stromme and Traut observed that the tumours sometimes contained mucus secreting or serous epithelium and granulosa or thecal elements. In the following case glomeruloid structures and micro cysts lined by flat epithelial cells with bulging nuclei like those of "mesonephromas", were striking features in a tumour in which a variety of other structural variants was present.



FIG 242—Case IX Mesonephroma (× 60)

Case IX—A woman of 52 had recently noticed abdominal enlargement. At operation a right ovarian tumour was removed. This was 15 centimetres in diameter, had a fibrous outer capsule and consisted of a single large cavity with slightly turbid watery contents enclosed by a tumour wall measuring up to 2 centimetres thick from which nodules of growth projected into the cavity. **Histology** (Figs 242 and 243)—The main cavity and many minute cysts in the solid growth were lined partly by flat epithelium with bulging nuclei and partly by cuboidal or low columnar epithelium these several variants being continuous with one another. Papillary ingrowths were present in many of the spaces and glomeruloid structures were abundant. Some papillary areas showed plentiful granular calcification others showed large clear cells and had a structure closely like that of renal carcinoma. Solid epithelial nests were also present and some of these closely resembled Walther or Brenner clumps. In the solid part of the growth the epithelial cysts and nests were set in an abundant cellular stroma consisting of closely packed plump spindle shaped cells resembling those of thecomas. This cellular stromal tissue showed transitions to the abundant, poorly cellular fibrous tissue which formed the main framework and capsule of the tumour.

(2) Heterotopic adrenal cortical tumours

In an excellent paper in 1921 Glynn concluded that there was no acceptable report of the presence of accessory adrenal tissue in the ovary, that all so called ovarian hypernephromas were structurally unlike adrenal cortical tumours that they were also functionally unlike them in not producing the sexual changes seen with adrenal tumours and that they were probably all luteal cell tumours. These conclusions still hold, no proven case of adrenal tumour of the ovary has yet been reported. None of the recent claims to have seen such tumours, e.g. those of Reis and Saphir is supported by adequate evidence. These growths are all luteinized ovarian tumours, and it must not be forgotten that luteinization may be seen in masculinizing growths as in Fig 240.

(3) Heterotopic renal tumours

Some writers, e.g. Saphir and Lackner, have described clear celled carcinomatous or hypernephroid tumours of the ovary, unaccompanied by masculinization which they suppose to be identical with renal carcinoma and to have arisen from renal elements included in the ovary. There is no evidence to support this assumption. Most 'hypernephroid' tumours are either luteal tumours or papillary cystic tumours with clear-celled areas (see Case IX below), while bulky metastases of renal carcinoma also occasionally occur in the ovaries and may simulate primary growths (Stadium Kannerstein *et al*). Young and Lowry's diagnosis of 'renal blastocytoma' of the parovarium in a woman of 45 is, I think, very doubtful.

(4) Schiller's mesonephroma

In 1939 Schiller described cystic tumours in which he detected 'glomeruli', glomerular like structures and abortive renal tubules', and which he supposed to have arisen from mesonephric tissue included in the ovary. While many subsequent writers accepted as a distinct entity the kind of tumour described by Schiller its mesonephric origin was disputed and several other equally speculative opinions were advanced e.g. that it was a papillo endothelioma (Kazancigil *et al*) or a 'teratoid cystadenoma' (Stromme and Traut).

From the literature of the subject (most of which is of a poor standard descriptively) and from my own examination of several specimens of supposed mesonephroma not only am I of the opinion that these views regarding its histogenesis are unfounded but I very much doubt if it is a distinct entity. Schiller's 'glomeruli' and abortive renal tubules are highly imaginary. Similar structures can be found in many an adeno papillary growth not only of the ovary but of the prostate, bowel, thyroid or breast. The appearance of the low cells with bulging nuclei lining the small cysts in the tumours does not warrant sharp separation of these from other papillary growths. Once again as so often before in the history of oncology a mere habit of growth resulting in a superficial resemblance of tumour tissue to some normal structure has led to an unfounded and unnecessary assumption of origin from aberrant tissue.

It is noteworthy that several writers on mesonephromas have recorded the presence in these growths of structures relating them to other well known ovarian tumours. Schiller's Figure 18 shows the typical intracystic papillary growth of a

Case XII—A Scotch collie aged 6 years had had a vaginal discharge for 6 weeks. An ovarian tumour and enlarged uterus were removed by operation. pyometra was present in lower uterine segment and in upper end of one horn. Opposite ovary was replaced by tumour 10 centimetres in diameter consisting of areas of solid yellowish growth between a honeycomb of cysts up to 2 centimetres in diameter with watery contents. *Histology*—Solid epithelial masses and epithelial sheets lining cystic spaces, consisting of large irregular polyhedral cells many of which are vacuolated. The appearance is that of a granulosa-cell growth with advanced luteinization.

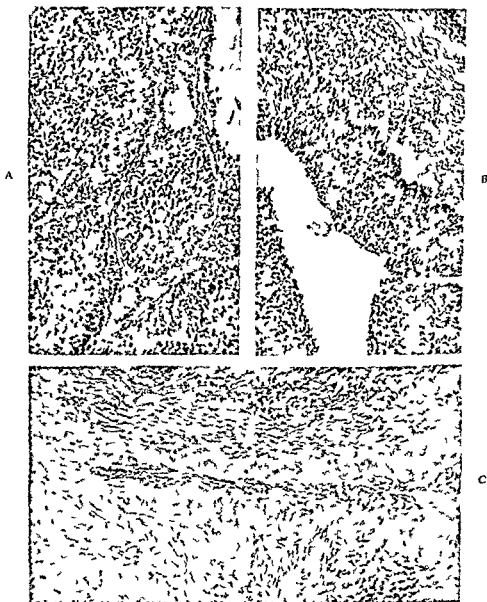


FIG. 245.—*Case XIII*. Ovarian tumour from a mare. A and B show granulosa-cell clumps and layers. C = folded hyaline bands like those of corpus albicans in a theca-cell area of the growth ($\times 120$).

Case XIII—A racing mare 6 years old had had irregular oestrus for several years and more recent debility and abdominal enlargement and was destroyed. *Necropsy*—Abdominal cavity contained many gallons of blood stained fluid. right ovary was replaced

This tumour was thus of great interest in showing not only the relationships of structures supposed to typify mesonephroma but also other structural variants showing an alliance with ordinary papillary cystadenoma with "hypernephroid" tumours with Brenner tumours and with theca cell tumours

SUMMARY OF PERSONAL CONCLUSIONS REGARDING THE HISTOGENESIS OF OVARIAN TUMOURS

He would be a bold man who in the present immature state of our knowledge, would dogmatize regarding the origins and interrelationships of the many and

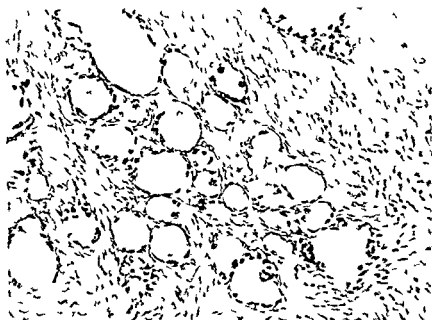


FIG. 243—Case 1A. Mesonephroma. Note the small cysts lined by flat cells with bulging nuclei and abundant cellular stroma ($\times 120$)

diverse types of ovarian tumours. But the evidence discussed in this chapter appears to me to show plainly—(a) that with exceptions so rare as to be negligible all the kinds of tumours described arise from the gonadal tissues themselves and not from included heterotopic tissues and (b) that many or all of the several kinds of growths are interrelated and that various structural combinations are frequent. In my belief our views of this difficult field are clarified by assuming that the several differentiated components of the normal ovary—the follicular epithelium, thecal tissue, luteal tissue, corpus fibrosum and the "germinal" epithelium—are all produced during adult life from the multipotent ovarian parenchyma or stroma. That many of the tumours take origin not from an already differentiated particular derivative, but from this formative parenchyma and exhibit divergent differentiation and maturational changes like those of the normal ovary and that the diversity of structure seen in different tumours and often in one tumour arises from this divergent differentiation and maturation

- Kazancigil T R, Laqueur W and Ladewig P (1940) *Amer J Cancer*, 40 199
- Kelsey H A (1945) *Brit Med J*, ii 922
- King E S J (1929) *Surg Gyn Obst* 49 433
- Kirshbaum J D and Newman B (1943) *Amer J Obst Gyn* 45 337
- Klaften E (1933) *Zbl Gynak*, 57 736
- Lepper E H (1935) *Proc Roy Soc Med*, 28 1645
- Lepper E H, Baker, A H and Vaux D M (1932) *Proc Roy Soc Med*, Sec Obst Gyn 25 45
- Ley G (1920) *Proc Roy Soc Med Sec Obst Gyn* 13 95
- LÖFFLER, E, and PRIESFL, A (1932) Bindegewebige Gewächse des Eierstockes von besonderer Bauart (Fibroma thecocellulare xanthomatodes ovarii), *Beitr path Anat* 90 199 (Excellent descriptions and figures of 6 theca-cell tumours)
- Marwil T B and Beaver D C (1942) *Amer J Obst Gyn* 43 99
- McIntyre W K (1942) *J Obst Gyn* 49, 41
- Mechler E A and Black W C (1943) *Amer J Path* 19 633
- MEYER, R (1931) The pathology of some special ovarian tumors and their relation to sex characteristics, *Amer J Obst Gyn* 22 697 (Summarizes his views refers to his previous papers and includes some good photomicrographs)
- Nicholson G W (1909) *Z Geburts Gynak* 64 252
- Nicholson G W (1923) *Guys Hosp Rep* 73 37 and 298
- NORRIS, E H (1938) Arrhenoblastoma *Amer J Cancer*, 32, 1 (A good general account and critique)
- Novak, E (1941) *Gynecological and Obstetrical Pathology* Philadelphia
- Novak E and Brawner J N (1934) *Amer J Obst Gyn* 28 637
- Novak E and Jones H W (1939) *Amer J Obst Gyn*, 38 872
- Novak E, and Long J H (1933) *J Amer Med Assoc* 101 1057
- Pemberton F A (1940) *Amer J Obst Gyn* 40 751
- Potter E B (1946) *Amer J Path* 22 551
- Powell C, and Black W C (1940) *Amer J Obst Gyn* 40 318
- Ragins A B and Frankel L (1940) *Amer J Obst Gyn* 40, 302
- Reis R A, and Saphir O (1938) *Amer J Obst Gyn*, 35 954
- Rewell R E (1942) *Guys Hosp Rep* 91, 163
- ROBINSON, M R (1930) Primary and secondary ovarian cancer *Surg Gyn Obst* 51 321 (A valuable paper expressing sound histogenetic principles and opposing the derivation of tumours from embryonic rests)
- Sailer S (1940) *Amer J Cancer* 38 473
- SAMPSON, J A (1938) Implantation carcinoma of the tubal mucosa secondary to carcinoma of the ovary, *Amer J Path* 14 385 (A beautifully illustrated study)
- Saphir O and Lackner J E (1944) *Surg Gyn Obst* 79 539
- Schiller W (1939) *Amer J Cancer* 35 1
- Schlottbauer C F (1939) *J Amer Vet Med Assoc* 95 181
- SCOTT, R B (1942) Serous adenofibromas and cystadenofibromas of the ovary *Amer J Obst Gyn* 43 733 (An excellent account of this special type of serous growth)
- SEEGAR, G E (1938) Ovarian dysgerminoma *Arch Surg* 37 697 (The best review of the subject)
- SHAW, W (1933) The pathology of ovarian tumours *J Obst Gyn* 40 257 (A good discussion regarding histogenesis)
- Southam A H (1928) *Brit Med J* i 661
- Stadium M L (1937) *Amer J Surg* 37 312
- Stohr G (1942) *Amer J Obst Gyn* 43 586
- Stromme W B and Traut H F (1943) *Surg Gyn Obst* 76 293
- Taylor H C and Alsop W E (1932) *Amer J Cancer* 16 1305
- TRAUT, H F, and BUTTERWORTH, J S (1937) The theca granulosa lutein cell tumors of the human ovary and similar tumors of the mouse's ovary *Amer J Obst Gyn* 34 987 (A useful general account with good figures)
- Traut H F, Kuder A and Cadden J F (1939) *Amer J Obst Gyn* 38 798
- TRAUT, H F, and MARCHETTI, A A (1940) A consideration of so called 'granulosa and theca cell tumors of the ovary *Surg Gyn Obst* 70 632 (A valuable study of the interrelationships and life history of these growths)

by huge cystic tumour weighing 20 pounds and consisting of multiple cysts up to 3 centimetres in diameter containing bloody fluid with intervening areas of white solid or finely cystic growth. *Histology* (Fig 245)—Typical granulosa and theca-cell tumour consisting of large solid and cystic masses of granulosa epithelium with intervening undifferentiated cellular theca-cell tissue merging into fibrous tissue. In many places typical follicle like arrangement of granulosa epithelium theca interna and theca externa is seen. Hyaline bands like those of corpora fibrosa are plentiful in the stromal tissues.

The 3 tumours from dogs are of interest not only because they show papillary and granulosa cell structures resembling those of human tumours but also because more than any human material they suggest kinship of these two kinds of growths. Further careful studies of canine and other animal ovarian tumours are needed.

REFERENCES

- ARNOLD W KOERNER, J and MATHIAS I (1930) Zur Pathologie der Gewächse mit morphogenetischen Einflüssen. *Virchows Arch* 277 48 (An excellent account of a remarkable case of oestrogenic tumour)
- Bankart A S B (1925) *Proc Roy Soc Med Orthoped Sec* 19 12
- Benecke E (1935) *Virchows Arch* 294 38
- Bettinger H (1933) *Frankfurt Z Path* 45 238
- Bettinger H F Lawson D F and Warden R (1945) *Med J Austral* 1 10
- Bland P B and Goldstein L (1935) *Surg Gyn Obst* 61 250
- Bland Sutton J (1922) *Tumours Innocent and Malignant* p 624 London
- Boltuch S M (1940) *Amer J Obst Gyn* 39 857
- Brenner F (1907) *Frankfurt Z Path* 1 150
- Burrows H (1943) *J Obst Gyn* 50 430
- Burrows H (1945) *Biological Actions of Sex Hormones* Cambridge
- BÜTTNER A (1932) Über Eierstockgeschwulste mit Vermännlichung (Arrhenoblastome, R Meyers) *Virchows Arch* 287 452 (A useful review)
- Danforth D N (1942) *Amer J Obst Gyn* 43 984
- Dockerty M B (1940) *Amer J Obst Gyn* 39 434
- Erdheim J (1930) *Virchows Arch* 275 383
- Evans H T and Strachan G I (1932) *Brit Med J* 1 519
- Feldman W H (1932) *Neoplasms of Domesticated Animals* pp 301-303 Philadelphia
- FOX R A (1942) Brenner tumor of the ovary *Amer J Path* 18 223 (A good review)
- FURTH J and BUTTLERWORTH J S (1936) Neoplastic diseases occurring among mice subjected to general irradiation with x rays II Ovarian tumors and associated lesions *Amer J Cancer* 28 66 (A well illustrated account of an important research)
- Geist S H (1942) *Ovarian Tumors* New York
- Geist S H Gaines J A and Pollack A D (1939) *Amer J Obst Gyn* 38 786
- Gibson H J C and Findlay G M (1923) *J Obst Gyn* 30 204
- Glynn E E (1912) *Quart J Med* 5 157
- CLYNN F F (1921) A comparison between ovarian hypernephroma and luteoma and suprarenal hypernephroma *J Obst Gyn* 28 23
- HARVEY W I DAWSON I K and INNES J R M (1939) Granulosa-cell tumour of the ovary *Edinb Med J* 46 256 (Contains a valuable series of photographs)
- Heesch O (1928) *Virchows Arch* 268 290
- HENDERSON D N (1942) Granulosa and theca cell tumors of the ovary *Amer J Obst Gyn* 43 194 (A well illustrated account of 30 tumours)
- Hicks J D (1941) *Med J Austral* 11 671
- Joest F and Ernesti S (1915) *Z Krebsforsch* 15 1
- Jolles B and Gleave H H (1945) *J Path Bact* 57 435
- von Kahlen C (1893) *Zbl all em Path* 6 257
- Kannerstein M Brown C R and Rosen J A (1943) *Amer J Obst Gyn* 46 290
- Kante A F and Klawans A H (1940) *Amer J Cancer* 40 474

CHAPTER 30

CARCINOMA OF THE FALLOPIAN TUBE

INTRODUCTION

THE PATHOLOGY of tubal carcinoma has been confused by two prevalent errors, namely (a) the incorrect microscopical diagnosis of carcinoma in cases of tuberculous salpingitis, and (b) the incorrect diagnosis of secondary growths in the tubes as primary ones. These two sources of error make doubtful the correctness of the diagnosis in not a few reported cases, and partly vitiate statistical and other generalizations regarding this disease.

As to (a), many writers on the subject, from von Franque (1911) to Novak (1941), have stressed that the epithelial proliferation accompanying tubal tuberculosis may easily be mistaken for carcinoma. I myself have made this mistake on two occasions, diagnosing coexistent tuberculosis and carcinoma on sections which, reviewed in the light of further experience, I am now quite satisfied show tuberculosis only. When the tuberculous changes are plentiful and obvious these will serve to warn against a too hasty diagnosis of disorderly epithelial changes as cancerous. Sometimes however pronounced epithelial proliferation occurs with little or no microscopical evidence of tuberculosis in the same area and an erroneous diagnosis of carcinoma may be made even by an experienced pathologist. In such a case, the absence of genuine cellular anaplasia and of distinct infiltration of the surrounding tube wall by the supposed growth should arouse suspicion and should lead to careful search of sections from other parts of the tube for signs of tuberculosis or of unmistakable carcinoma.

As to (b), namely the confusion of primary with secondary carcinoma of the tube, Orthmann, who was the first to describe tubal carcinoma in 1888, was also the first to insist that secondary disease of the tube from primary carcinoma of the ovary or uterus is frequent and may easily be mistaken for primary tubal carcinoma. In cases like the following in which papillary growth is present in both tube and ovary, I believe it is often impossible to determine the primary site with certainty.

Case I—Surgically removed tissues from a sterile married woman of 69 years consisted of (a) *right ovary and tube*—the tube normal but the ovary represented by a smooth lobulated mass $6 \times 4 \times 3$ centimetres partly cystic and partly composed of masses of friable white growth. (b) *left ovary and tube*—the outer two thirds of the tube distended to a diameter of 3 centimetres by masses of white papillary growth which also protruded through the abdominal ostium and the ovary $10 \times 8 \times 6$ centimetres and like its fellow in structure. (c) several large fragments of friable growth which lay free in the abdominal cavity. Microscopically all of the growths showed similar active adenocarcinoma of cystic papillary type (Fig 246). Sections of the broad ligaments, ovarian pedicles and right tube showed no growth and uterine curettage some weeks later gave simple endometrial tissue only. It was not possible to decide whether the case was one of bilateral cystadenocarcinoma of the ovaries with a metastatic implant in the tube, or of primary tubal carcinoma with ovarian metastases.

- Walthard M (1903) *Z Geburts Gynak* 49 233
- WERDT, F (1914) Über die Granulosazellumoren des Ovariums *Beitr path Anat*, 59 453 (An excellent account)
- Werth (1884) *Arch Gynak*, 24 100
- Willis R A (1934) *The Spread of Tumours in the Human Body* London
- Young J S and Lowry C G (1934) *J Path Bact*, 39 179

Ages -	-	-	25-	30-	35-	40-	45-	50-	55-	Over 60
Cases -	-	-	3	6	23	41	44	32	22	6
Percentages -	-	-			13	23	25	18	13	

Thus nearly one half of the patients were in the fifth decade, and two thirds of them were between 40 and 55 years of age. The youngest was 27 years old.

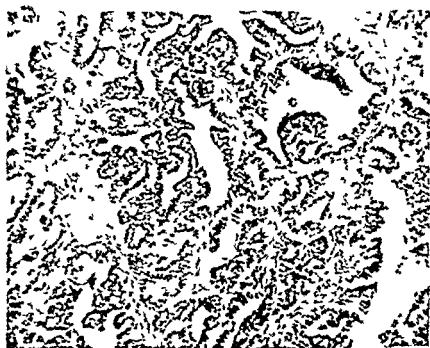


FIG 247 —Case II Papillary adenocarcinoma of the tube ($\times 105$)

(3) Marital state, parity

Of the 196 patients reviewed by Wechsler, if miscarriages are disregarded, 47 (i.e. 32 per cent) had never borne children, 147 had been pregnant, and of these 43 had had only one child. In many cases the last pregnancy had occurred many years before the development of the growth.

RELATION TO SALPINGITIS

Doran, Wechsler and others have believed that tubal carcinoma is often preceded by pelvic inflammatory disease. Some more recent writers, e.g. Ewing, endorse this view, while others, e.g. Novak, doubt it. The evidence for the former opinion, as outlined by Wechsler was as follows: (a) although a history of pelvic inflammation was seldom recorded in the cases reviewed by him, his figures, cited above denoting a relative degree of sterility in the subjects of tubal carcinoma suggested that previous salpingitis had often been present, (b) the frequent association of tubal carcinoma with tubo ovarian cyst, and the



FIG 246—*Case 1* Papillary adenocarcinoma of either tubal or ovarian origin ($\times 105$)

It is probable that unrecognized primary growths other than ovarian or uterine may also produce confusing secondary disease of the tubes. I have seen a pair of surgically removed tubes both of which were evenly thickened and which the microscope unexpectedly showed to be diffusely infiltrated by signet ring-cell carcinoma like that of the Krukenberg tumour, suggesting primary gastric carcinoma. In another case excised tubes diagnosed at operation as bilateral pyosalpinx were found to be distended by large masses of solid growth which also infiltrated the tube walls and surrounding tissues. Microscopically this was a poorly differentiated spheroidal celled carcinoma with nothing to suggest its origin. In such a case while a provisional diagnosis of tubal carcinoma may be made this diagnosis cannot be held to be certain unless subsequent necropsy proves the absence of a primary growth elsewhere. Kaufmann saw massive distension of both tubes by mucoid carcinoma of gastric origin.

These then are the reasons for accepting, only with reserve the following generalizations regarding carcinoma of the Fallopian tube.

INCIDENCE

(1) Frequency

Tubal carcinoma is a rare disease accounting for less than 1 per cent of all female genital cancers (Martzloff). Orthmann who reported the disease for the first time in 1888 found 84 cases on record in 1906. In 1926 Wechsler found 196 reported cases and by 1940 Martzloff found over 360.

(2) Age

Wechsler's review of 177 cases of specified age showed the following age distribution.

In the meantime, an open mind must be preserved on the question as to whether tuberculosis of the tube, or other kinds of salpingitis may evoke neoplastic change in some cases. An answer to this question might well be attainable by a more thorough microscopic study of the tumours and of the other parts of both tubes in all cases of tubal carcinoma. Such a study might show that inconspicuous tuberculosis or other inflammation is more commonly present than is revealed by examination of only a few sections of the growth.

SITUATION AND STRUCTURE

Wechsler found that of 183 cases the tumours were right sided in 64, left-sided in 62, and bilateral in 57. Later writers also are agreed that the growths are bilateral in about one third of the cases. They usually occupy the outer or middle portions of the tube the uterine end of which is often unaffected, so that the enlarged organ is pear-shaped with its narrow stalk situated medially. That the outer parts of the tube are most often affected accords with the distribution of epithelium in the organ the outer parts of which contain abundant folded mucosa while the mucosa of the inner third is relatively scanty. Many of the growths project from the fimbriated opening into the peritoneal cavity as friable papillary or cystic grape like masses. Not seldom the growth is related to a tubo-ovarian cyst in which case it is often difficult to distinguish between tumours of tubal and ovarian origin.

The microscopic structure

Most tumours are distinctly papillary and cystic cavities with intra cystic papillary formations may be present as in Case II. Areas of solid epithelial growth may often be seen in parts. While parts of the best differentiated tumours may show an epithelial pattern closely resembling that of normal Fallopian mucosa the structure is never distinctive enough to permit confident microscopic distinction between tubal and ovarian papillary carcinoma. Designation of the best differentiated growths as adenomas or papillomas, as suggested by Doran by Bland Sutton and by other earlier writers is not justified. 'Papillomas' should not be regarded as distinct from carcinomas but merely as the most highly differentiated, and therefore least malignant, members of the entire group.

SPREAD AND METASTASIS

The tumours soon reach the peritoneal cavity either by direct extension through the abdominal ostium or by invasion through the tube wall. Spread to the ovaries or pelvic peritoneum then occurs and widespread trans coelomic dissemination often ensues as in Case II. Metastatic deposits in the pelvic or abdominal lymph glands are commonly present at operation or necropsy though it is likely that as with endometrial carcinoma lymph nodal metastases are often absent as long as the growths are confined within the tube itself. Unfortunately this early stage of the disease is seldom seen by the surgeon who usually finds the tumours in an advanced inoperable stage. The prognosis in general is therefore bad and permanent cures are seldom obtained. The least unfavourable

not uncommon presence of hydrosalpinx of the opposite tube, also pointed to earlier inflammatory disease, and (c) all four of Wechsler's own cases showed evidence of such disease.

While it is true as already noted that an incorrect diagnosis of tubal carcinoma has sometimes been made in cases of tuberculous salpingitis the coexistence of genuine carcinoma with tuberculosis has been reported by several writers, e.g. by von Franke by Callahan *et al* (1929) and by myself (Willis 1934). My case was as follows.



FIG 248—Case II From a peritoneal metastasis ($\times 105$)

Case II—History—For 1 year before her death a married woman aged 38 years suffered from abdominal enlargement and recurrent ascites which laparotomy showed to be due to tubal carcinoma with extensive peritoneal metastases. **Necropsy** showed large cystic distension of the right tube 12 centimetres in diameter lined by masses of ragged papillary growth, which projected through the abdominal opening of the tube and also extended through its wall in several places. Widespread deposits of growth and adhesions were present in all parts of the peritoneal cavity and the spleen and liver were directly invaded from the deposits on their capsules. The inguinal iliac lumbar coeliac mediastinal and right and left cervical lymph glands contained large deposits of tumour and the cisterna chyli and thoracic duct were closely invested but apparently not invaded. There were no blood borne metastases in the viscera. **Histology**—In all situations the tumours consisted of cellular adenocarcinoma with many mitoses showing papillary structure in many places (Figs 247 and 248). Sections of the less distended part of the tube towards its uterine end showed in addition to growth areas of typical caseating tuberculous tissue with many giant cells and Ziehl-Neelsen's stain revealed many tubercle bacilli. No tuberculous tissue was found in any of the metastatic growths.

Whether the coexistence of tubal carcinoma and tuberculosis is due to the former predisposing to the latter or vice versa or is purely fortuitous cannot be decided until a statistically significant number of proved cases has accumulated.

CHAPTER 31

EPITHELIAL TUMOURS OF THE UTERUS

THE MAIN subject of this chapter is uterine carcinoma. Some of the localized *endometrial and cervical polypi* are, no doubt, *benign tumours*—*papillomas* or *adenomas*—but it is difficult or impossible to separate these from the diverse forms of hyperplasia to which the uterine epithelia are liable. In a concluding section we will consider those rare uterine tumours in which both epithelial and non epithelial tissues participate.

SOME GENERAL ASPECTS OF UTERINE CARCINOMA

By far the best treatise yet written on the pathology of cancer of the uterus is that of Cullen (1900). This excellent work contains detailed histories and descriptions of many specimens of carcinomas of all types and hundreds of unsurpassed illustrations of their gross and microscopic structure by Max Brodel and Hermann Becker. Hurdon's monograph (1942) is a useful outline from the clinical standpoint.

Since cervical and corporeal carcinoma are aetiological and structurally quite distinct diseases, we will consider them separately. But since mortality statistics do not separate them, we must first briefly survey the frequency of uterine carcinoma in general as disclosed in these statistics and other figures.

(1) Mortality rates, and race incidence of uterine cancer

In all countries with mortality statistics, carcinoma of the uterus appears as one of the three commonest causes of death from cancer in women, the other two being in most countries carcinoma of the stomach and carcinoma of the breast. The mortality figures collected by Hoffman (1915) show that during the early years of this century, in some countries, e.g. England and Wales and Australia, uterine cancer was the commonest form of fatal malignant disease in women, that in most other European countries and in the United States of America it was second to carcinoma of the stomach, and that in all countries with reliable mortality figures, uterine cancer caused more deaths than mammary cancer. Thus in England and Wales from 1908 to 1912, carcinoma of the uterus accounted for 19,673 out of 99,818 cancer deaths in females, i.e. 20 per cent, as compared with 17 per cent from carcinoma of the breast and 14 per cent from carcinoma of the stomach. In Switzerland 1901 to 1910, carcinoma of the uterus caused 3,299 out of 22,593 female deaths from cancer, i.e. 15 per cent as against 35 per cent from carcinoma of the stomach and 10 per cent from carcinoma of the breast. In the United States of America, 1908 to 1912 cancer of the stomach and liver accounted for 34 per cent, cancers of the genital organs for 26 per cent, and cancer of the breast for 16 per cent, of cancer deaths in females.

Probably owing mainly to a real increase in the frequency of carcinoma of the breast, more recent mortality figures show reversal of the positions of uterine and

growths are those which appear at operation to be confined to the tube or which even though they may project at the fimbriated opening are removed intact and are found to have a uniformly high degree of histological differentiation Bland Sutton described surgical cures in both kinds of case

Blood borne metastases in the liver lungs or elsewhere are rare

REFERENCES

- Bland Sutton J (1922) *Tumours Innocent and Malignant* p 467 London
 Callahan W P Schiltz F H and Hellwig C A (1929) *Surg Gyn Obst* 48 14
 Doran A (1904 1910) *J Obst Gyn* 1904 6 285 1910 17 1
 Ewing J (1940) *Neoplastic Diseases* p 670 Philadelphia
 von Franque O (1911) *Z Geburts Gynak* 69 409
 Kaufmann E (1929) *Pathology* p 1600 (Reimann's translation) Philadelphia
 Martzloff K H (1940) *Amer J Obst Gyn* 40 804
 Novak E (1941) *Gynecological and Obstetrical Pathology* p 236 Philadelphia
 ORTHMANN E G (1888) Ueber Carcinoma tubae *Z Geburts Gynak* 15 212
 ORTHMANN E G (1906) Zur Kenntnis der malignen Tubenneubildungen *Z Geburts Gynak* 58 376 (Orthmann not only reported the first case of primary carcinoma but also gave valuable accounts of secondary carcinoma of the tubes)
 WECHSLER, H F (1926) Primary carcinoma of the Fallopian tube *Arch Path* 2 161 (The best review of the subject)
 Willis R A (1934) *The Spread of Tumours in the Human Body* p 430 London

because the precise point of origin of some adenocarcinomas of the lower uterine segment, whether endometrial or endocervical, is uncertain

Estimates of the relative frequency of the three types of carcinoma vary considerably, but broadly it may be said that cervical carcinoma is three or four times as common as endometrial and that cervical epidermoid carcinoma is at least ten times as common as cervical adenocarcinoma. Cullen's carefully studied series of 182 cases of uterine cancer comprised 128 epidermoid carcinomas of the cervix, 35 adenocarcinomas of the corpus, and 19 adenocarcinomas of the cervix. Norris and Vogt's series comprised 346 cervical carcinomas to 115 corporeal carcinomas, the latter thus forming 25 per cent of the total. (Novak cites Norris and Vogt's figure incorrectly as 15 per cent, this percentage was of *all* cancers of the female genital tract.) Hurdon's records covered 1340 cases of carcinoma of the cervix and 269 of the body of the uterus. My own histological material from consecutive hospital cases covers 174 cases of uterine carcinoma (144 surgical and 30 necropsy cases) which comprised 111 epidermoid carcinomas of the cervix, 56 endometrial adenocarcinomas, and 7 adenocarcinomas of the cervix, i.e. 64.32 and 4 per cent respectively. Many of the older estimates of the frequency of corpus carcinoma are much lower than those just cited, often between 5 and 15 per cent (Lane-Clayton, Kaufmann, Novak). This difference is no doubt largely attributable to the improved diagnosis of corporeal carcinoma during the last few decades, especially as the result of the more regular use of diagnostic curettage with microscopical examination, but it may also be partly due to a real increase in the relative frequency of endometrial carcinoma, related to its conjugal and age incidence (*see below*).

It is necessary to mention here the extraordinary statements made by Williams in his book on uterine tumours (1901), that of 160 consecutive uterine carcinomas only 4 were of the corpus and that most of his cervical carcinomas were of the cylinder-celled 'glandular' type. Such a palpable error on the part of an oft-quoted authority raises doubts of the dependability of all his statements on histological and statistical matters.

The estimated frequency of cervical adenocarcinomas varies widely, ranging in different series from 1.6 to 11.7 per cent of cervical cancers, with an average of 5.7 per cent (Norris).

(4) Uterine carcinoma in animals

Uterine carcinoma is one of the less frequent forms of malignant disease in animals, but has been seen in the rabbit, rat, mouse, guinea pig, horse, ox, dog, lioness, boar, gazelle, rhinoceros and fawn (Feldman). In all but one of these species, however, the uterus is a rare site of carcinoma; many reported series of carcinomas in animals contain only occasional examples or none at all of uterine origin. Thus in the collection of 250 consecutive tumours in animals made by Rudduck and myself there is not an example of uterine carcinoma. The exceptional species is the rabbit, in which endometrial adenocarcinoma is the most frequent form of tumour (Polson, Twort, Burrows, Orr and Polson). Many of the growths in other species also are endometrial adenocarcinomas, but in a few cases the tumours have been cervical in origin, e.g. squamous-celled carcinoma in a gazelle (Petit, cited by Murray), and papillary adenocarcinoma

mammary cancer is causes of death in England and Wales and in most other English speaking communities (see Chapter 13 and comparison tables by Hurdon). In England at present, uterine carcinoma causes about 12 per cent, and mammary carcinoma about 20 per cent, of the female deaths from cancer.

As to the races with no reliable mortality records there is nevertheless good evidence that in these also uterine cancer is one of the commonest forms of malignant disease. Medical practitioners in China and India find carcinoma of the cervix a frequent form of cancer there. Of 1,830 cases of carcinoma in Hindu women 888 (48 per cent) were of the genital tract and of 666 cases in Moslem women in India, 223 (33 per cent) were genital (Nath and Grewal 1935, 1937 and 1939). Of 119 deaths from cancer in the Chinese of both sexes in Hong Kong from 1895 to 1904, 14 were due to uterine cancer, of 51 cases of cancer in Hawaiians 15 were of the uterus and of 1,223 cases of cancer in coloured Cubans 347 (28 per cent) were of the female genitalia (Hoffman). The uterus is the commonest site of carcinoma in native women of the East Indies (Snyders and Straub Bonne), thus in 243 cancer necropsies on Malays and Chinese in Java and Sumatra, Bonne found 31 cases of uterine carcinoma of which 25 were in Malays. Cervical cancer is frequent in the Chinese of Hainan (Bercovitz, 1941), in American negroes (Cullen Quinland and Cuff) and in Nigerian natives (Smith and Elmes). There is good evidence that cancer of the uterus is less frequent in Jews than in non Jews of the same community (Hoffman, Sorsby Smith).

(2) Mortality from uterine cancer in relation to age and conjugal state

We shall see later that carcinoma of the cervix and carcinoma of the corpus differ markedly in both their age incidence and their relation to conjugal state and parity. Here however, something must be said of the age distribution of uterine carcinoma as a whole and its relation to conjugal state as disclosed by mortality statistics. The 76th Annual Report of the Registrar General for England and Wales (1915) contained an informative analysis of the deaths from uterine cancer for the 3 years 1911 to 1913 setting out the standardized mortality rates for the successive 5 year age periods from 25 onwards for both single and married or widowed women. This analysis showed clearly (a) that for both the single and married groups the mortality rate rose throughout life until old age, when there was a slight falling off in the rate (b) that at all age periods the mortality rates for married women decidedly exceeded those for single women the differences being much more marked before than after the age of 50 and (c) that the standardized rate for all ages over 15 years was 73 per cent greater for the married than for the single. Further analysis of age distribution and relation to conjugal state and parity is best made from accurate clinical records and with respect to the three main types of carcinoma now to be discussed.

(3) The three types of uterine carcinoma and their relative frequency

Carcinomas of the uterus fall into three groups—(1) epidermoid carcinoma of the cervix (2) endometrial adenocarcinoma of the corpus and (3) adenocarcinoma of the cervix. Groups (1) and (2) are quite distinct in their incidence structure and behaviour. Group (3) is less sharply separable from group (2).

EPITHELIAL TUMOURS OF THE UTERUS

(3) Mode of origin, pre-cancerous and early cancerous changes

Most epidermoid carcinomas of the cervix arise directly from the stratified epithelium of the external os or the portio vaginalis (Fig 249) Occasionally

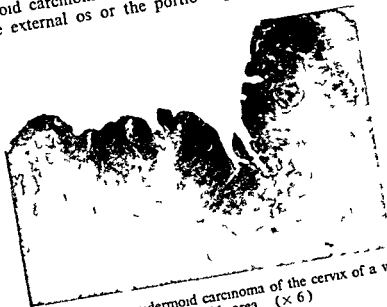


FIG 249 —Very early superficial epidermoid carcinoma of the cervix of a woman of 40 The tumour is of uniform depth over a considerable area ($\times 6$)

the origin may be from metaplastic stratified epithelium formed within the cervical canal or glands or in an endocervical polypus (Fig 250)

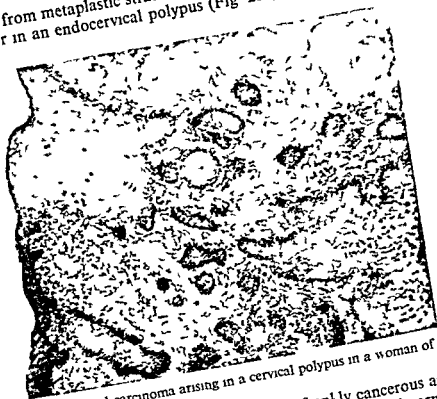


FIG 250 —Early epidermoid carcinoma arising in a cervical polypus in a woman of 48 ($\times 80$)

In addition to early growths which are already frankly cancerous and invasive when they first come under notice, there occur also various abnormal changes in the cervical epithelium the possible pre cancerous proclivities of which must

in a rhinoceros (Betke) Bullock and Curtis described squamous celled carcinomas of the uterus in rats

EPIDERMOID CARCINOMA OF THE CERVIX UTERI

(1) Age incidence

The age distribution of cervical carcinoma is similar in all European countries and in America and the collected results of 7381 cases (Lane Claypon 1927) showed the following approximate percentages in successive 5 year periods

Ages	Under 30	30~	35~	40~	45~	50~	55~	60~	65~	Over 70
Percentages	4	9	16	20	19	15	9	5	2	1

Thus about two fifths of the cases were in the fifth decade, and the mean age was 46 years. The ages recorded in many other individual series of cases (Cullen Pack and Le Fevre and my own) are in close agreement with this the maximal number of cases occurring in the fifth decade and the mean age of onset falling between 45 and 50 years—47 in my own series. This mean age is earlier by several years than in most other classes of carcinoma namely of the breast stomach intestine oesophagus and mouth in all of which the mean ages of onset lie between 50 and 59 (Greenwood 1926). In more than one half of the cases cervical carcinoma commences in the age period 40-55. It shows no relationship to the menopause, the mortality curves rising steadily to old age. It is rarely seen under the age of 25, but has been recorded in minors (Diddle) it is also rare after 65. Patients in the younger age groups show neither lower operability nor worse prognosis than older patients (Lane Claypon). The mean duration of untreated cases is about 21 months (Lane Claypon, Greenwood).

(2) Marital state, parity, menstrual history

It has long been recognized that carcinoma of the cervix is less frequent in single and nulliparous than in parous women. Thus of Cullen's 50 cases with the necessary details recorded all were married and only one was childless. Of 7986 cases collected by Lane Claypon only 170 (2.1 per cent) were single. Lane Claypon and McCullagh found that about 9 per cent of cases of cervical carcinoma were nulliparous. These figures contrast sharply with those for carcinoma of the corpus (see below).

While parity thus decidedly predisposes to cervical cancer the number of pregnancies appears to be immaterial. Lane Claypon's analysis showed that the incidence of the disease was no greater amongst mothers of many children than amongst mothers of few or only one and also that miscarriages did not specially predispose to cervical carcinoma. The previous menstrual histories of patients show no significant differences from those of non-cancerous women.

Occasional early specimens of cervical carcinoma afford evidence, similar to that described for the skin and lip, that the growth has arisen, not from a single minute focus but from a considerable field of epithelium (Fig 249). Even in already well-established growths, histological evidence that cancerous change of the neighbouring epithelium is still in progress may sometimes be seen, as in several of Cullen's carefully studied cases e.g. that depicted in his Fig 42. Clear instances of cervical carcinoma of multicentric origin have not so far been described. There is need of further careful studies of the mode of origin of early carcinomas in this region by serial sections and reconstructions.



FIG 251—Great cellular and nuclear pleomorphism in epidermoid carcinoma of the cervix ($\times 80$)

(4) Structure

As in other sites epidermoid carcinoma of the cervix may appear as a projecting papillary growth, or as an infiltration of the underlying tissues with early surface ulceration, or as a combination of these two. Brodel's and Becker's drawings in Cullen's book fully illustrate the various gross and microscopic appearances of the tumours.

Microscopic structure

Although distinct epidermoid differentiation of some degree is to be found in most of the growths they present a wide range of histological appearances. The degree of keratinization, the size and shape of the cell clumps, and the characters of the cells and their nuclei, all vary greatly. Cornification in the form of well defined cell nests is less frequent than in oral and epidermal carcinomas, but patchy irregular keratin formation is frequent. The cell clumps are often large and of triangular, lentiform or irregular outlines in section, fine tendril-like growth of the epithelium is rare. The structural peculiarities of the individual

be considered. These include hyperplastic and metaplastic changes accompanying cervicitis, erosions, polypi and leucoplakia. The earlier literature and views on this subject were well outlined in 1916 by Stone, who gave examples of the various 'pre cancerous' lesions and who concluded that 'for each type of fully developed carcinoma there is a corresponding type of benign and intermediary change'. Schiller (1928) also depicted many examples of suspicious cervical lesions discovered by routine examination of excised uteri, and he concluded that these were indeed early carcinomas comparable with Bowen's disease of the skin. Smith and Pemberton described 16 early cervical carcinomas.

However, the pre cancerous potentialities of histologically suspicious changes have certainly been exaggerated. Squamous metaplasia of the endocervical epithelium and encroachments of the metaplastic epithelium into the cervical glands producing appearances resembling early carcinomatous invasion are common and are innocuous in the great majority of cases. Carmichael and Jeaffreson found such changes in 40 per cent of adult cervixes attributed them to both hormonal and local factors, and rejected the view that they are pre cancerous. Close familiarity with the histological variations possible in normal and damaged cervixes at all ages is necessary before attempting to assess the significance of suspicious epithelial changes in this region. Undoubtedly many of the supposedly 'pre cancerous' lesions of the cervical epithelia are harmless and the distinctive characters of the truly pre cancerous states have yet to be defined.

The infrequency of epidermoid carcinoma of the cervix in nullipara strongly suggests, as Cullen said, 'that the injuries incidental to labour have a potent influence on the development of this variety of cancer'. Very plausibly then tears, erosions and cervicitis have been postulated as the exciting or predisposing factors. However, this proposition also is far from established. The acknowledged rarity of carcinoma of the cervix of the prolapsed uterus shows that simple mechanical irritation and persistent mild inflammation are in themselves not important factors in the causation of cervical carcinoma. Nor is there any evidence that venereal infections predispose to this disease. It seems likely then that the parous uterus is prone to the development of cervical carcinoma for some more specific reason than the mere presence of the effects of trauma or chronic inflammation. The factors concerned are still obscure but that hormonal as well as local factors may be concerned is strongly suggested by the experimental production of cancer of the cervix in mice by prolonged oestrogen administration (see Chapter 4, Section V). The suggestion that coitus may play a direct part lacks evidential support as does also the view that contraceptive practices may be partly responsible. That the development of carcinoma of the cervix is not dependent on the presence of the body of the uterus is shown by the frequency of this disease in the residual cervix after subtotal hysterectomy for myomas and other diseases. Buhney cites figures from various writers showing that stump carcinoma develops in between 0.1 and 6 per cent of cases of subtotal hysterectomy figures which show no clear evidence of either increased or diminished liability of the residual cervix to cancer. Simultaneous separate carcinomas of the cervix and corpus are occasionally seen. I have examined two specimens showing this coexistence.

Occasionally, however, diffuse spindle celled carcinoma may simulate sarcomatous appearances. There is no doubt that many cases of supposed "sarcoma" and 'endothelioma' of the cervix, such as those depicted in Cullen's Figs 102 to 104 and 178 and 179, have been instances of diffusely cellular or otherwise atypical carcinoma. Cullen himself, indeed, with scientific frankness, reported a case of squamous celled carcinoma of the cervix microscopically resembling sarcoma in places of which he said, 'were it not for sections from other portions of the growth in which the squamous-cell origin is clear, one would be justified in making a diagnosis of sarcoma'.

Some cervical carcinomas of rapid growth and poor keratinization show well defined rounded intra epithelial spaces, formed partly by fluid accumulation and partly by degenerated cells (Fig 253). cursory microscopical examination of such a tumour may easily lead to an erroneous diagnosis of 'adenocarcinoma', but closer inspection will show that the epithelial masses are of epidermoid type and that there is no true glandular orientation of the cells around the spaces.

The great cytological diversity exhibited by cervical carcinomas renders attempts at precise "grading" even more arbitrary and futile here than in other situations (Willis, 1931). While carcinoma cells may sometimes be identified in vaginal smears (Gates and Warren), I feel very dubious of the diagnostic reliability of this test in most cases.

Eosinophil leucocytes sometimes collect in great numbers in and around epidermoid carcinoma of the cervix (references, Willis, 1934), and occasionally pronounced eosinophilia of the blood also develops (Sala and Stein). Metaplastic ossification of the stroma of the growth, as in Reich's third case, is rare.

(5) Local spread

Following infiltration of the cervix itself, extension of the growths may take place in any direction. Extension downwards into the vaginal walls is frequent and necessitates removal of a liberal vaginal cuff in performing hysterectomy. Cranial extension into the body of the uterus sometimes effects almost complete replacement of the organ. Of great practical importance is the occasional growth which ascends far into the corpus without producing conspicuous changes in the portio vaginalis. The pelvic peritoneum may be reached by cranial extension and transcoelomic metastases may arise in this way. Lateral extension into the parametrial tissues is of great importance, since on its extent operability and prognosis largely depend. In advanced cases the growth reaches the walls of the pelvis and produces fixity of the viscera. Obstruction of the ureters is common and death is often due to ascending renal infection. Anterior and posterior spread involves the bladder and rectum, and fistulae of these are distressingly common in late stages of the disease. The invasion of pelvic veins by growth is sometimes demonstrable (Reich). Of occasional results of the direct spread of cervical cancer may be mentioned pyometra, sometimes perforating and causing peritonitis, direct spread from the parametrium to the tube or ovary, sometimes with invasion of ovarian cysts, contact invasion of adherent coils of intestine sometimes causing intestinal obstruction (Willis, 1931), and invasion of uterine myomas (e.g. Cullen's Figs 72 and 74).

cells are legion and often very diverse in one tumour, multinucleated cells and giant nuclei of bizarre shapes are common (Fig 251) Many tumours contain



FIG 252—Undifferentiated spindle-celled clumps in a cervical epidermoid carcinoma ($\times 96$)



FIG 253—Rounded spaces in a very cellular rapidly growing epidermoid carcinoma of the cervix these had led to an incorrect histological diagnosis of "adenocarcinoma" ($\times 300$)

glycogen rich clear cells a good description of which is that of Babes and Lazarescu Pantzu. Some tumours show a prominent spindle-celled structure the spindle cells usually forming well-defined epithelial clumps (Fig 252)

thoracic and cervical glands Estimates of the frequency of lymph nodal metastases vary widely In necropsy series they lie usually between 50 and 70 per cent, in surgical series between 25 and 45 per cent Thus Williams found lymph glands affected in 56 of 78 necropsy cases of uterine cancer (nearly all cervical) i.e. 72 per cent Of my 23 necropsy cases, 12 (52 per cent) showed discrete deposits in glands Bonney found glands affected in 42 per cent of operation cases From deposits in the upper lumbar lymph glands the thoracic duct may be invaded and, next to gastric carcinoma, uterine (mainly cervical) carcinoma is the most frequent invader of the duct, accounting for about one quarter of the cases (Willis, 1934) Main veins may be invaded from contiguous cancerous lymph glands, e.g. the inferior vena cava in one of my cases (1931, Case VII)

(b) *Metastases by the blood stream*

These are found in about one quarter of fatal cases, most commonly in the liver or lungs Metastasis to the liver probably occurs usually by the portal vein, following invasion of veins in the wall of the rectum or neighbouring peritoneum, the lungs are reached by way of the systemic veins or the thoracic duct Blood borne metastases in other parts are rare, but bones occasionally contain metastases, which may even mimic primary tumours (Williams, Kaufmann, Joll, Reich and other references by Willis, 1934)

(c) *Metastases in ovaries, tubes and vagina*

On rare occasions, apparently discrete secondary growths have been seen in the ovaries or tubes, e.g. by Borrmann, Cullen (Figs 78 and 84) Taussig Bell and Datnow, and Reich The route of origin of these deposits is uncertain and indeed it is usually difficult to be sure that they are indeed separate from the main tumour and not merely outcrops from inconspicuously infiltrated tissues When genuinely separate, they may have arisen either from venous or lymphatic emboli carried by aberrant routes because of obstruction of main vessels in the parametrial tissues, or from particles of tumour carried retrogradely within the lumen of the Fallopian tube, or by transcoelomic metastasis on the ovarian or tubal surfaces following extension of the primary growth to the serous surface of the uterus or to the pouch of Douglas Seemingly discrete nodules of growth, sometimes seen in the walls of the vagina are often not true metastases but merely outcrops from inconspicuous infiltration of the underlying tissues When really discrete they must be attributed to downward carriage of tumour emboli in veins or lymphatics following blockage of these vessels higher up, it is extremely improbable that implantation of tumour cells on the vaginal surface occurs

ENDOMETRIAL ADENOCARCINOMA OF THE CORPUS

(1) *Age incidence*

All statistics agree that corporeal carcinoma occurs decidedly later in life than cervical on an average about 8 years later (Cullen, Norris and Vogt,

The following remarkable case exemplifies slow extensive superficial spread of a cervical carcinoma in the endometrium, tubes and ovaries

Case 1 (Mr R Fowler's case)—*History*—In 1934 at age of 48 patient had uterine haemorrhages was curetted and found to have squamous-cell carcinoma of the cervical canal the growth consisting of thick layers of poorly cornifying stratified epithelium spreading over available surfaces but also invading subjacent tissues Radium was introduced with good local effect Patient then remained well until September 1944 when a lower abdominal mass was noticed the cervix appeared normal Laparotomy disclosed large right ovarian cysts and smaller left ovarian cyst adherent to tubes uterus appeared normal the tubes and cysts were removed *Naked-eye examination*—Right sided cysts 2 in number were 10 and 4 centimetres in diameter respectively joined by a waist of indurated tissue 1 centimetre thick and 3 centimetres



FIG. 254—*Case 1* The even layer of non-cornifying epidermoid carcinoma lining the right Fallopian tube ($\times 120$)

wide cysts were thin walled had smooth fibrous outer coats and were lined by a thin layer of irregularly corrugated papillary growth right tube was irregularly thickened in its outer half and adherent to smaller cyst wall Left sided cyst was 3 centimetres in diameter and generally similar to those on right side except that it showed some papillary projections from its outer surface attached tube was indurated but not enlarged *Micro-examination* unexpectedly revealed that the whole of both Fallopian tubes the larger right sided cyst and the left sided cyst were all lined by a layer of non-cornifying stratified epithelium resembling that of the cervical growth examined 10 years earlier (Fig. 254) Ovarian tissue was present on one side of each of the cysts which appeared to be tubo ovarian cysts developed as a result of the growth spreading out of the abdominal ostia of the tubes The smaller right sided cyst was lined by cubical epithelial cells and was probably a simple parovarian cyst (*Note*—The surgeon decided not to remove the uterus but to apply radiational treatment)

(6) Metastasis

(a) Lymph nodal metastases

In parametrial invasion both direct spread and embolic metastasis to lymph glands share Later the disease spreads to the lumbar inguinal and even the

(2) Marital state, parity, menstrual history

Unlike carcinoma of the cervix, corpus cancer often occurs in the single and nulliparous. Thus of 19 of Cullen's cases with the data recorded although 17 were married, 10 had never been pregnant, in Norris and Vogt's series 26 per cent were spinsters, Lane Claypon and McCullagh found not less than one third of all cases to be sterile for one reason or another, and in Miller's series, of 183 cases, 177 of whom were married, 48 (i.e. 27 per cent) had never conceived. Thus, while childbearing predisposes to carcinoma of the cervix, sterility or some factor related to it predisposes to endometrial carcinoma. The menstrual histories of subjects of this disease show no significant abnormalities.

(3) Inherited predisposition to corpus carcinoma

While the family histories of most cases of uterine carcinoma do not suggest any inherited tendency to the disease, some striking exceptions are recorded. The most remarkable of these is the 'Family G' first described by Warthin (1925), and later by Hauser and Weller (1936). In this family, in the course of three generations, 41 persons out of 174 aged 25 or more produced 43 carcinomas. All of the 20 cancers in males were gastro-intestinal, while the 23 cancers in females included 6 gastro-intestinal and 15 endometrial, no case of cervical carcinoma occurring.

(4) Pre-cancerous conditions in the endometrium

Lesions which have been held to predispose to endometrial carcinoma include endometritis, hyperplasias, polypi and myoma. Let us consider each of these.

(a) Endometritis

The suggestion of early writers that endometritis predisposed to cancer of the uterus was largely due to a misconception of what constituted endometritis. With increasing recognition of the distinction between true infective endometritis and non-inflammatory endometrial hyperplasias well outlined by Kaufmann, attention has shifted from the former to the latter as possible pre-cancerous states. There is no evidence that post-abortal, puerperal or venereal infections predispose to endometrial cancer, and the occasional coexistence of cancer and tuberculosis in the uterus (von Franqué, Gais) is probably merely coincidental.

(b) Endometrial hyperplasias

These form a large and diverse group doubtless related in most cases to hormonal disturbances, though the exact nature of these is often obscure. There are good grounds for believing with Novak (1941) and others that in some cases initially simple hyperplasia passes into carcinoma. This applies particularly to post-menopausal hyperplasias. The grounds for this belief are as follow: (i) As Kaufmann, Stone, Welsh, Novak and others have pointed out there is no sharp histological borderline between hyperplasia and carcinoma. While it is fortunately true that in the great majority of cases the microscopical diagnosis of one or the other can be made confidently, there occur cases in which the most experienced are unable to distinguish between extravagant atypical hyperplasia

Lane Claypon, Pack and Le Fevre) Thus, Norris and Vogt's series of 115 cases with a mean age of 53 showed the following age distribution

Decade	-	-	-	3	4	5	6	7	8
Number of cases -	-	-	1	14	18	57	21	4	

The mean age of Miller's 183 cases was 54, and of Pack and Le Fevre's cases 55, as compared with 48 years for carcinoma of the cervix. In my own series of 31 specimens from patients of recorded ages, the mean age was 57 years at the time of operation, compared with 48 for cervical carcinoma.

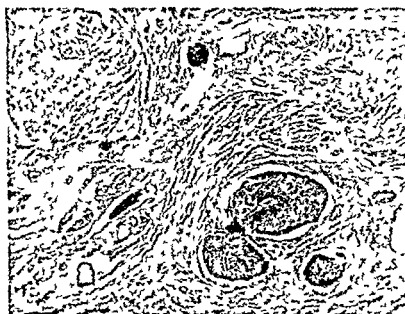


FIG. 255.—Case II. Solid carcinomatous clumps of an adenocarcinoma occupying small veins in the myometrium ($\times 60$).

Carcinoma of the corpus is rarely seen under the age of 30—the youngest of Norris and Vogt's series was 29 and the three youngest in my series were 25, 32 and 41. The disease has appeared, however, even in childhood and adolescence (Gilbert, Diddle). Unlike cervical carcinoma that of the corpus often appears after the age of 65—this applied to 9 of my 31 cases. The youngest patient in my series presented some other unusual features justifying a brief summary.

Case II—A single woman aged 25 who had had no menstrual abnormalities and who was otherwise in good health complained of lower abdominal discomfort of 3 months duration. Operation showed multiple uterine myomas the largest the size of a tennis ball. Subtotal hysterectomy was performed. Examination of the specimen unexpectedly revealed in addition to the myomas a bulky endometrial growth microscopically an active adenocarcinoma with areas of solid anaplastic growth which extended into the muscle and invaded small blood vessels (Fig. 255). In view of these features the patient remained well and with no signs of recurrence 5 years later.

carcinoma are found together at an early age, certainly support this idea. Careful statistical study of the frequency of the coexistence of myoma and carcinoma is needed before deciding whether this is wholly fortuitous or not.

(5) The mode of origin of endometrial carcinomas

There is good evidence that, as in many other epithelia, so in the endometrium, carcinoma often arises from a more or less extensive field of tissue sometimes perhaps the entire endometrium. (a) As already noted above, clear histological evidence of the progressive transformation of hyperplastic endometrium into



FIG. 256.—From a bulky endometrial carcinoma, showing the complex tubular pattern frequently seen in these growths ($\times 20$)

carcinoma is sometimes to be seen (Novak). (b) Specimens are not unusual in which much or the whole of the endometrium is replaced by a superficial layer of carcinoma with little penetration into the muscle, and it seems much more likely that these have arisen by an extensive cancerization of the endometrium *in situ* than by spread from a single small focus (Welsh). (c) Multiple foci of carcinoma are sometimes seen, these have been attributed to regional metastases in the endometrium (Kaufmann) but they more probably denote multifocal origin. Careful study of the endometrium and of early carcinomas in predisposed families, such as the "Family G", of Warthin would probably afford particularly clear evidence of the mode of origin of these tumours.

(6) Structure

Again Cullen's work provides an admirable atlas of the gross and minute anatomy of the disease. Many of the tumours are well differentiated columnar-celled adenocarcinomas often with convoluted tubular or papillary patterns (Fig. 256). Areas of solid epithelial masses are also common, and these or still more anaplastic diffusely cellular growth may form most of the tumour. However

and commencing carcinoma (ii) Hyperplasia and carcinoma may coexist with apparent transitions from one to the other. Novak depicted examples and stated that he had observed the coexistence in nearly one quarter of his cases of adenocarcinoma. Early adenocarcinoma has been observed arising in an extensively hyperplastic endometrium (Fluhmann and Stephenson). Kaufmann referred to cases of intramural adenocarcinoma arising from the epithelium of adenomyoma, i.e. that type of endometrial hyperplasia now called *endometriosis interna*. Oldfield and Stewart also described an example of carcinomatous *endometriosis interna*, and I have seen a closely similar specimen. (iii) In rare cases cited by Fluhmann and Stephenson repeated curettings have shown at first only hyperplasia but later carcinoma. (iv) By analogy with other organs under endocrine control such as the breast prostate and ductless glands themselves it would be surprising if atypical hyperplasias of the endometrium did not at times become neoplastic. While much experimental investigation of the endometrial overgrowths produced by excessive oestrogens has been carried out we still await elucidation of all the hormonal and local factors responsible for human endometrial hyperplasias and for determining the transition to neoplasia in some cases. The predisposition of single and childless women to endometrial carcinoma as compared with cervical carcinoma is no doubt related in some way to the unphysiological life of the unproductive uterus.

(c) *Endometrial polypi*

Polypi are an occasional source of carcinomas (Iseki, cited by Novak). Malignant change in a previously benign polypus must be distinguished from carcinoma beginning as a localized polypoid growth. When cases of this kind and polypi of doubtful malignancy are excluded very few examples of carcinoma commencing in polypi will remain. If we look upon polypi as benign tumours—adenomas or papillomas of the endometrium—then malignant change in them parallels that seen in polyposis of the stomach or intestine. If we look upon polypi as localized hyperplasias then supervening carcinoma will appear as a special instance of the sequence discussed in the previous paragraph.

(d) *Myomas*

The coexistence of uterine myoma and carcinoma has frequently been noted (many examples by Cullen) and when the carcinoma has occupied the endometrium immediately overlying a projecting submucous myoma the temptation has been strong to suppose that the latter has induced the former. But in view of the great frequency of uterine myomas (perhaps in about 20 per cent of women over 30) we must strongly suspect their coexistence with carcinoma to be only coincidental in most cases. However an indirect relationship between the genesis of myoma and of endometrial carcinoma is quite possible. It is not unlikely that uterine myomas are related to hormonal disturbances in which oestrogens play a part and we have just noted the pre-cancerous potentialities of some endometrial hyperplasias many of which also are certainly the result of hormonal disturbances. Perhaps then in some cases of coexisting myoma and carcinoma both tumours may owe their genesis to a common hormonal factor. Cases like No II above in which multiple large myomas and endometrial

of such areas only. It is significant that no cases of pure epidermoid carcinoma of the endometrium have been recorded of recent years. Kaufmann has given a valuable outline of squamous metaplasia in uterine carcinomas, and of the possible relationships of carcinomas to previous squamous metaplastic changes in the uterus. In my opinion squamous metaplasia in the endometrium should always be regarded as carcinomatous.

Some endometrial carcinomas are so anaplastic that little or no trace of glandular differentiation is to be found. Descriptively we must call these "carcinoma simplex", though of course it is not implied that they are essentially any different save in degree of anaplasia, from the adenocarcinomas. Usually such growths consist of polyhedral cells arranged in recognizably epithelial clumps, but sometimes they become quite diffuse in structure. Elsewhere (1931 and 1932) I have given instances of the way in which anaplastic areas of uterine adenocarcinomas may become diffusely cellular, simulating sarcoma microscopically. The same topic is discussed and well illustrated in a valuable paper by Tudhope and Chusholm, who emphasize the wide range of structure possible in anaplastic endometrial carcinomas and who rightly doubt the genuineness of many supposed instances of sarcoma and carcinosarcoma of the uterine cavity. In his Fig. 78, Nicholson (1924) depicted cartilaginous metaplasia in the stroma of an endometrial carcinoma.

(7) Growth and local spread of endometrial carcinoma

In their early stages many carcinomas are quite superficial and largely confined to the endometrium itself over a small or large area. As Novak pointed out, and as I myself have repeatedly confirmed, it is not unusual for diagnostic curettage to lead to a microscopic diagnosis of undoubted carcinoma, hysterectomy to be performed soon afterwards, and for careful examination of the uterus to fail to discover any residual growth. Of course it must not be concluded from such cases that curettage alone has indeed eradicated the growth, undiscovered residues may be present in parts not examined, for serial microscopic examination of an entire uterus is impracticable. In other cases, when curettage has been less complete, minute residues of tumour, still, however, confined to the endometrium may be found in the excised uterus. In one such specimen, in which no residual tumour could be found in the uterine cavity, I discovered a small cancerous focus in the myometrium close to the entry of a Fallopian tube.

In more advanced stages the tumour may spread over much or the whole of the endometrial surfaces, distend the cavity, penetrate to a variable depth into the muscle, and produce enlargement of the uterus. Direct extension into one or both Fallopian tubes may take place. The tumours may also spread downwards in the cervical canal and may protrude into the vagina. Uterine myomas may be invaded (see Cullen's Fig. 433).

Deep invasion of the muscle and extension to the peritoneal surfaces and to the parametria are late, usually irremediable, stages of the disease, often accompanied by great enlargement of the uterus, spread to neighbouring organs and metastases in lymph glands or peritoneal cavity. Rectal and vesical fistulae are much less frequent than with cervical carcinoma.

no distinction in nomenclature between the variants is called for they are all endometrial carcinomas with varying degrees of differentiation. In particular as Kaufmann rightly insisted the old self-contradictory name "adenoma malignum" still retained by some writers for the best differentiated members of the group (as by Ewing) should be discarded.

One variety of structure seldom mentioned shows areas of clear cells and closely resembles clear-celled papillary adenocarcinoma of the kidney. The nature of the change in the cytoplasm which produces this appearance is uncertain, it is not due to the presence of mucus and selective stains for glycogen or fatty substances have been inapplicable to the few paraffin-embedded specimens which I have examined.



FIG. 257.—Islands of squamous epithelium in the glandular spaces of an endometrial adenocarcinoma from a woman of 63 ($\times 60$).

Epidermoid metaplasia is a frequent change in parts of the tumours (Fig. 257). It was observed in 9 of my 50 cases a proportion closely similar to Miller's figure of 15 per cent. Nicholson (1923) found squamous epithelium in 14 of 36 endometrial carcinomas. Such tumours have often been called 'adenoacanthomas' or 'adeno-canceroids'. In behaviour and prognosis they differ little if at all from other endometrial carcinomas. Some earlier writers on uterine carcinoma described examples of what they believed to be pure squamous called carcinomas of the corpus e.g. Gebhard (1892), Fleischlen (1895) and Emanuel (1895). While it is not impossible that predominantly or even exclusively epidermoid carcinoma of the endometrium may occur this diagnosis can of course be sustained only after thorough microscopic study of all parts of the tumour and after exclusion of the possibility that a cervical carcinoma has extended up into the corpus as Emanuel admitted may have happened in his case. These early workers were not aware of the frequent occurrence of areas of squamous metaplasia in adenocarcinomas of the uterus and they may have been misled by microscopic study

(c) *Transperitoneal metastasis*

Once the tumour has reached the peritoneal surface at any point either of the uterus itself or by the transtubal route, metastasis to other parts of the peritoneum readily takes place. Discrete peritoneal metastases are present in about one half of fatal cases.

(d) *Metastasis by the blood stream*

With rare exceptions, blood borne metastases appear only late in the course of the disease. They are present in only about one quarter of fatal cases. The organs most often affected are the lungs, liver and bones. The metastases are rarely of any clinical importance but occasionally those in bones create diagnostic difficulties. Thus Kaufmann mentioned a case with widespread metastases in which the only symptoms had been pains due to spinal deposits.

(e) *Metastases in the vagina and vulva*

These have been described by many writers, e.g. Cullen (Figs 218-9) Strachan and Spencer, and have often been attributed to surface implantation. I also have seen apparently discrete vaginal nodules which could plausibly have been supposed to have arisen in this way. It is, however, very doubtful whether such grafting of tumour particles on the vaginal surface ever occurs. As Kaufmann, Milner, Sampson, Leitch and others have insisted for cervical cancer, lymphatic extensions of the growth into the vaginal walls are frequent, and this applies also to advanced corporeal growths. Outcrops from these extensions or from embolic tumour particles arrested in lymphatics or small veins in the subepithelial tissues are undoubtedly the source of most or all of the supposed vaginal implants from uterine cancers, endometrial and cervical alike. Spencer described two remarkable cases of endometrial carcinoma with metastases in the vagina and vulva, treated by operation and radiation, and free of recurrence after 10 and 13 years respectively.

ADENOCARCINOMA OF THE CERVIX

Since the exact site of origin of growths within the cervical canal or isthmus is seldom known, and since adenocarcinomas are seldom of such distinctive histological structure that the specific nature of their parent glandular tissue is clear, the scope of the name adenocarcinoma of the cervix is uncertain. Strictly it should refer only to tumours arising from the cervical glandular epithelium proper, but there is little doubt that there have often been included in this class endometrial adenocarcinomas of the isthmus or lower part of the body which have spread downwards into the cervix. The only tumours the genuine cervical origin of which is sure are (a) those in which the endometrium of the isthmus is demonstrably uninvolved and (b) those the microscopic structure of which clearly resembles cervical rather than endometrial glandular tissue, especially mucus secreting growths. It is also possible that some adeno papillary growths of the cervix may arise not from the cervical glands proper, but from the neighbouring remains of Gartner's duct (see a report by Wolfe and further discussion in the next chapter). These uncertainties as to precise origin must be borne in mind when reading accounts of "cervical adenocarcinomas", the best of which are those of Cullen and Norris.

(8) Metastasis

In general endometrial carcinoma metastasizes relatively late. Metastasis in the five following ways must be considered (a) by lymphatics (b) by the Fallopian tubes, (c) by the peritoneal cavity, (d) by the blood stream, (e) by surface implantation in the vagina

(a) *Metastasis by lymphatics*

Deposits in lymph glands are usually absent as long as the tumour remains confined to the uterine cavity or extends only superficially into the muscle, but they are often present when the muscle is deeply invaded, or the tumour has reached the parametrium or peritoneum. The glands first affected are those of the hypogastric iliac and lower lumbar groups. Extension to more cranial groups may follow but in general this is less pronounced than with cervical carcinoma and involvement of the cisterna chyli and thoracic duct is rare. Many authorities e.g. Novak, have believed lymphatics to be the principal route of metastasis to the tubes and ovaries but while this may be admitted for some cases my own findings satisfy me of the greater importance of the tubal route, now to be described

(b) *Metastasis by the Fallopian tubes*

Kundrat, Werner, Sampson, Offutt and others have advanced clear evidence that detached fragments of carcinoma of the fundus of the uterus may pass into the lumina of the tubes to be implanted there or on the ovaries or pelvic peritoneum. I have seen several specimens which convince me that this is a frequent mode of metastasis of fundal carcinoma. Thus in one case a surgically excised uterus contained a large adenocarcinoma which involved the cornua and uterine ends of both tubes. The surfaces of both ovaries presented many raised nodules up to 3 millimetres in diameter, histological study of which showed them to be adenocarcinomatous implants mounted on the surface of the ovaries. The substance of which was clear of growth. In another surgical specimen the fundus was distended by a large adenocarcinoma which invaded the muscle but nowhere reached the peritoneum and which involved the medial ends of both tubes. The remainder of the tubes and the broad ligaments and mesovaria were clear of growth and thus was confirmed microscopically. Each ovary was replaced by a single thin walled serous cyst, and on the surface of the cystic right ovary just below the fimbriated end of the tube there was a single pedunculated nodule of adenocarcinoma 4 millimetres in diameter. In yet another case the fundus contained a friable adenocarcinoma which extended only slightly into the muscle. The lumen of the middle part of the right Fallopian tube was occupied by a discrete nodule of growth 8 millimetres in diameter and the right ovary and adjacent omentum contained large multiple masses of secondary growth. In my opinion so real is the risk of transtubal metastasis from fundal carcinoma that the surgeon performing hysterectomy for this disease should (a) make a special search for early metastatic nodules seeded on the ovaries, fimbriae or neighbouring peritoneum, discovery of which will decidedly affect prognosis and (b) exercise all possible care during the operation to avoid undue pressure on the uterus and tubes so minimizing the risk of expressing fragments of growth from the tubes into the peritoneal cavity.

(c) Transperitoneal metastasis

Once the tumour has reached the peritoneal surface at any point, either of the uterus itself or by the transtubal route, metastasis to other parts of the peritoneum readily takes place. Discrete peritoneal metastases are present in about one half of fatal cases.

(d) Metastasis by the blood stream

With rare exceptions, blood-borne metastases appear only late in the course of the disease, they are present in only about one quarter of fatal cases. The organs most often affected are the lungs, liver and bones. The metastases are rarely of any clinical importance, but occasionally those in bones create diagnostic difficulties. Thus Kaufmann mentioned a case with widespread metastases in which the only symptoms had been pains due to spinal deposits.

(e) Metastases in the vagina and vulva

These have been described by many writers, e.g. Cullen (Figs. 218-9) Strachan and Spencer, and have often been attributed to surface implantation. I also have seen apparently discrete vaginal nodules which could plausibly have been supposed to have arisen in this way. It is, however, very doubtful whether such grafting of tumour particles on the vaginal surface ever occurs. As Kaufmann, Milner, Sampson, Leitch and others have insisted for cervical cancer, lymphatic extensions of the growth into the vaginal walls are frequent and this applies also to advanced corporeal growths. Outcrops from these extensions or from embolic tumour particles arrested in lymphatics or small veins in the subepithelial tissues are undoubtedly the source of most or all of the supposed vaginal implants from uterine cancers, endometrial and cervical alike. Spencer described two remarkable cases of endometrial carcinoma with metastases in the vagina and vulva treated by operation and radiation, and free of recurrence after 10 and 13 years respectively.

ADENOCARCINOMA OF THE CERVIX

Since the exact site of origin of growths within the cervical canal or isthmus is seldom known and since adenocarcinomas are seldom of such distinctive histological structure that the specific nature of their parent glandular tissue is clear the scope of the name 'adenocarcinoma of the cervix' is uncertain. Strictly it should refer only to tumours arising from the cervical glandular epithelium proper, but there is little doubt that there have often been included in this class endometrial adenocarcinomas of the isthmus or lower part of the body which have spread downwards into the cervix. The only tumours the genuine cervical origin of which is sure are (a) those in which the endometrium of the isthmus is demonstrably uninvolved and (b) those the microscopic structure of which clearly resembles cervical rather than endometrial glandular tissue especially mucus secreting growths. It is also possible that some adeno papillary growths of the cervix may arise not from the cervical glands proper, but from the neighbouring remains of Gartner's duct (see a report by Wolfe and further discussion in the next chapter). These uncertainties as to precise origin must be borne in mind when reading accounts of 'cervical adenocarcinomas' the best of which are those of Cullen and Norris.

(1) Frequency

Norris's paper tabulates many reported series of cases of cervical carcinoma, totalling 9 509 cases of which 542 (i.e. 5.7 per cent) were adenocarcinomas. The percentage in different series however differed greatly, from 1.6 to 11.7, owing no doubt to the uncertain limits of the group. Griffin found 94 of 749 cervical carcinomas (12.6 per cent) to be of glandular type.

(2) Age

The average age of Norris's 43 cases was 47; two thirds of them were in the fifth and sixth decades and the youngest was 28. Cullen also found the disease to occur most often between the ages of 45 and 50 years.

(3) Marital state

Of 13 of Cullen's cases 12 were married and had borne children. Of Norris's 43 patients 38 were married or widowed and 80 per cent had been pregnant or had had operations on the cervix. Unlike endometrial adenocarcinoma, there is no evidence that sterility predisposes to cervical adenocarcinoma.

(4) Macroscopic appearance

This varies widely: the tumours may be ulcerated, papillary, nodular or diffusely infiltrating and they may arise in the vaginal part of the cervix, within the cervical canal or intramurally.

(5) Microscopic structure

Norris's many excellent figures sufficiently show the wide range of structure and the impossibility of making any useful sub-division of the group. Tumours of mingled epidermoid and glandular structure, adenoacanthomas, are rare. Mucus secretion by the tumour cells also appears to be infrequent but when it is present it affords the most substantial evidence of the genuinely cervical origin of the tumour. Elsewhere (1931) I have recorded an example of well-differentiated mucoid adenocarcinoma of the cervix and Griffin described two cases of this kind. Cullen described an unusual case of mucoid adenocarcinoma widely involving both cervix and corpus with great enlargement of the uterus.

(6) Growth and metastasis

In behaviour and prognosis the tumours more closely resemble cervical epidermoid carcinoma than endometrial adenocarcinoma. In many cases there is early infiltration of the cervix, spread to the parametria and metastasis to regional lymph glands. However again the uncertain limits of the group make it futile to attempt to generalize about its behaviour or to calculate the frequency of metastasis. In the only case of undoubted cervical adenocarcinoma on which I performed necropsy referred to above the large growth had directly invaded the appendix and ileum; there were metastases in the lumbar and mesenteric lymph glands, the right iliac vein was invaded by growth and blood-borne metastases were present in the lungs.

UTERINE TUMOURS CONTAINING BOTH EPITHELIAL AND NON EPITHELIAL TISSUES

The lesion formerly spoken of as 'adeno myoma' is no longer regarded as a neoplasm but as a hyperplastic extension of the endometrium into the myometrium accompanied by hypertrophy or hyperplasia of the muscle—adenomyosis or endometriosis interna. However, true tumours containing both epithelial and muscular neoplastic tissues do occasionally occur, for both components may reappear in metastases. Thus Hart reported the case of a woman aged 72 who had had a large uterine tumour removed 22 years previously, and who was found at necropsy to have multiple small well defined tumours in the lungs, careful search failed to discover any other primary growth, and microscopically



FIG 258—Case III Pulmonary metastasis with structure of adeno myoma ($\times 120$)

the pulmonary nodules presented the typical structure of fully differentiated "adeno myoma" with glandular acini and small cysts embedded in smooth muscular tissue. The following personally studied case was similar to Hart's, except that the primary growth in the uterus had become sarcomatous.

Case III—History—A woman aged 58 underwent subtotal hysterectomy for fibroids the tumours were not examined microscopically. The patient returned to hospital 3 months later with a large recurrent tumour in the pelvis and died 2 months after this. *Necropsy*—A large necrotic growth filled the pelvis and there were scattered metastases in the peritoneum and in the iliac lymph glands from which the tumour had invaded the inferior vena cava. The lungs contained a few small firm white well defined spherical nodules. *Histology*—Many parts of the pelvic growth and its peritoneal metastases were examined and all showed anaplastic spindle celled sarcoma devoid of epithelial elements. The lung nodules (Fig 258) showed well differentiated epithelial acini lined by cubical or low columnar cells set in abundant smooth muscular and fibrous tissue.

(1) Frequency

Norris's paper tabulates many reported series of cases of cervical carcinoma totalling 9 509 cases of which 542 (i.e. 5.7 per cent) were adenocarcinomas. The percentage in different series however differed greatly from 1.6 to 11.7 owing no doubt to the uncertain limits of the group. Griffin found 94 of 749 cervical carcinomas (12.6 per cent) to be of glandular type.

(2) Age

The average age of Norris's 43 cases was 47—two thirds of them were in the fifth and sixth decades and the youngest was 28. Cullen also found the disease to occur most often between the ages of 45 and 50 years.

(3) Marital state

Of 13 of Cullen's cases 12 were married and had borne children. Of Norris's 43 patients 38 were married or widowed and 80 per cent had been pregnant or had had operations on the cervix. Unlike endometrial adenocarcinoma there is no evidence that sterility predisposes to cervical adenocarcinoma.

(4) Macroscopic appearance

This varies widely—the tumours may be ulcerated, papillary, nodular or diffusely infiltrating and they may arise in the vaginal part of the cervix within the cervical canal or intramurally.

(5) Microscopic structure

Norris's many excellent figures sufficiently show the wide range of structure and the impossibility of making any useful sub-division of the group. Tumours of mingled epidermoid and glandular structure, adeno-acanthomas, are rare. Mucus secretion by the tumour cells also appears to be infrequent but when it is present it affords the most substantial evidence of the genuinely cervical origin of the tumour. Elsewhere (1931) I have recorded an example of well-differentiated mucoid adenocarcinoma of the cervix and Griffin described two cases of this kind. Cullen described an unusual case of mucoid adenocarcinoma widely involving both cervix and corpus with great enlargement of the uterus.

(6) Growth and metastasis

In behaviour and prognosis the tumours more closely resemble cervical epidermoid carcinoma than endometrial adenocarcinoma. In many cases there is early infiltration of the cervix, spread to the parametria and metastasis to regional lymph glands. However again the uncertain limits of the group make it futile to attempt to generalize about its behaviour or to calculate the frequency of metastasis. In the only case of undoubted cervical adenocarcinoma on which I performed necropsy referred to above the large growth had directly invaded the appendix and ileum, there were metastases in the lumbar and mesenteric lymph glands, the right iliac vein was invaded by growth and blood-borne metastases were present in the lungs.

examination—The uterine cavity was distended by a mass of firm papillary and finely cystic growth 5 centimetres in main diameter which sprang by a broad base from the fundus replacing almost the whole of the endometrium of the upper two thirds of the organ. The growth was well demarcated from the uterine muscle which though thicker than normal was unaffected. *Histology* (Fig 259)—The growth had a coarsely papillary structure the papillae being clothed by endometrial epithelium and containing many multiplying glandular acini and cysts. The stromal tissue was everywhere abundant and cellular consisting partly of undifferentiated compact spindle-celled growth partly of less compact stellate celled growth like mucoid embryonic tissue and partly of differentiating bundles of smooth muscle fibres with all transitions between them. Mitoses were fairly numerous. Areas of mature fibrous and myomatous tissue also were present.

In this case the bulky tumour clearly had a purely endometrial origin. The epithelial acini and cysts were endometrial, and the intervening undifferentiated and smooth muscular tissue occupied the place of a greatly overgrown endometrial stroma and had no demonstrable connexion with the myometrium. The neoplastic muscle was developing by metaplastic transformation of the undifferentiated stroma. Such a transformation loses something of its novelty when we come to study the purely mesenchymal mixed tumours of the uterus, which also arise in the endometrium, and in which as we shall see later, striated muscle, cartilage, bone, adipose and mucoid connective tissue all appear.

It is possible then that the tumour of Case IV affords a connecting link between the true adeno myomas and the non epithelial mixed tumours of the uterus. It may be that an adeno myoma—or its malignant counterpart—is of purely endometrial origin and is that particular variety of mixed tumour which is composed of neoplastic endometrial epithelium and neoplastic smooth muscular tissue, the differentiation of the latter from the plastic stroma perhaps being determined by the very presence of the former. Nicholson (1918) described a remarkable specimen of multiple mixed tumours of the endometrium in which the non epithelial components comprised mucoid tissue, cartilage, adipose tissue and muscle and the epithelial component was cancerous and appeared along with the non epithelial tissues in metastases. Those endometrial mixed tumours which contain no neoplastic epithelium but are composed of a variety of mesenchymal derivatives are described further in Chapter 48.

REFERENCES

- Babes A. and Lăzărescu Pantzu (1930) *Virchows Arch* 275 765
 Behney C. A. (1940) *Amer J Obst Gyn* 40 780
 Bell, W. B. and Datnow M. M. (1932) *Amer J Cancer* 16 1
 Bercovitz N. (1941) *Cancer Res* 1 154
 Betke R. (1911) *Frankfurt Z Path* 6 19
 Bonne C. (1935) *Amer J Cancer* 25 811
 Bonney V. (1932) *Brit Med J* ii 914
 Bornmann R. (1932) *Virchows Arch* 284 623
 Bullock F. D. and Curtis M. R. (1930) *J Cancer Res* 14 1
 Burrows H. (1940) *J Path Bact* 51 385
 CARMICHAEL R. and JEAFFERSON B. I. (1941) Squamous metaplasia of the columnar epithelium in the human cervix. *J Path Bact* 52 173 (A valuable well illustrated account)
 CULLEN T. S. (1900) *Cancer of the Uterus*. London. (An unsurpassed collection of case reports with many excellent illustrations of the gross and microscopic structure of the tumours by Max Brodel and Hermann Becker.)

Comment—Evidently sarcomatous change had occurred in a uterine adeno myoma which had already produced small metastases of benign mixed type in the lungs

We might reasonably assume that in such tumours the muscular component has arisen from the myometrium. But that this is not necessarily so is shown by

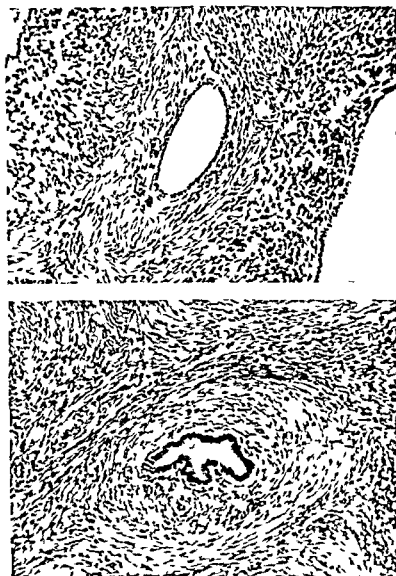


FIG 259—Case II. Endometrial mixed tumour containing epithelium lined spaces separated by cellular stromal tissue with abundant differentiating smooth muscle ($\times 120$)

the following unusual case in which a mixed tumour containing both epithelial and muscular tissue seems clearly to have come from the endometrium alone

Case II (Dr D M Seeley's case)—*History*—A woman aged 70 had noticed dysuria for 3 months and examination showed that this was due to firm incarceration of a greatly enlarged uterus in the pelvis. She had had 3 children uneventfully, no miscarriages, a normal menstrual history and an uneventful menopause. During operative removal of the uterus it was noted that the ovaries, tubes and peritoneum were normal. *Naked-eye*

- Spencer, H (1932) *Proc Roy Soc Med* 26 257
 Stone W S (1916) *Surg Gyn Obst*, 23 248
 Strachan, G I (1930) *Proc Roy Soc Med*, 24 117
 Taussig F J (1907) *Surg Gyn Obst* 5 511
 TUDHOPE, G R, and CHISHOLM, A E (1934) On the so-called sarcoma of the endometrium *J Obst Gyn* 41 708 (An important demonstration of misleading microscopic structure displayed by anaplastic endometrial carcinoma)
 Twort C C (1937) *J Path Bact* 44 492
 Warthin A S (1925) *J Cancer Res* 9 279
 Welsh D A (1929) *J Coll Surg Austral* 2 254
 Werner P (1913) *Arch Gynak* 101 725
 Williams W R (1901) *Uterine Tumours* London
 Willis R A (1931) *Med J Austral* ii 293
 Willis R A (1932) *Med J Austral*, ii 65
 Willis R A (1934) *The Spread of Tumours in the Human Body* London
 Wolfe S A (1940) *Amer J Obst Gyn* 39 312

- Diddle A W (1940) *Amer J Cancer* 39 207
- Emanuel (1895) *Z Geburts Gynak* 32 477
- Ewing J (1940) *Neoplastic Diseases* Philadelphia
- Feldman W H (1932) *Neoplasms of Domesticated Animals* Philadelphia
- Flaschlen N (1895) *Z Geburts Gynak* 32 347
- Fluhmman C F and Stephenson H A (1929) *Surg Gyn Obst* 48 425
- von Franque O (1911) *Z Geburts Gynak*, 69 409
- Gais E S (1926) *Arch Path* 1 542
- Gates O and Warren S (1945) *Amer J Path* 21 567
- Gebhard C (1892) *Z Geburts Gynak* 24 1
- Gilbert J B (1932) *Amer J Obst Gyn* 24 402
- Greenwood M (1926) *Rep Pub Health Med Subj* No 33 London
- Griffin M A (1938) *J Path Bact* 46 379
- Hart C (1912) *Frankfurt Z Path* 10 78
- Hauser I J and Weller C V (1936) *Amer J Cancer* 27 434
- Hoffman F L (1915) *The Mortality from Cancer Throughout the World* Newark New Jersey
- Hurdon E (1942) *Cancer of the Uterus* London
- Joll C A (1923) *Brit J Surg* 11 38
- KAUFMANN, F (1929) *Pathology* (Translation by Reimann) Philadelphia (Contains a good account of uterine carcinoma)
- Kennaway E L and Kennaway N M (1937) *Acta Internat Union against Cancer* 2 101
- Kundrat R (1906) *Arch Gynak* 80 384
- LANE CLAYTON Janet E (1927) *Cancer of the uterus A statistical inquiry into the results of treatment being an analysis of the existing literature Rep Pub Health Med Subj* No 40 London (A valuable discussion of many statistical aspects of uterine cancer)
- Lane Clayton J E and McCullagh W M H (1927) *Rep Pub Health Med Subj* No 47 London
- Leitch A (1922) *Brit Med J* 1 604
- Miller N F (1940) *Amer J Obst Gyn* 40 791
- Milner R (1904) *Arch klin Chir* 74 669 and 1009
- Murray J A (1908) *Imp Cancer Res Fund Sci Rep* p 41
- Nath V and Grewal K S *Indian J Med Res* 1935 23 149 1937 24 633 1939 26 785
- Nicholson G W *Gay's Hosp Rep* 1918 69 173 1923 73 298 1924 74 81
- NORRIS, C C (1936) *Adeno-carcinoma of the cervix Amer J Cancer* 27 653 (A good account with many excellent microphotographs)
- Norris C C and Vogt M E (1924) *Amer J Obst Gyn* 7 550
- Novak E (1927) *Amer J Obst Gyn* 14 470
- Novak E (1941) *Gynecological and Obstetrical Pathology* Philadelphia
- Offutt S R (1932) *Surg Gyn Obst* 54 490
- Oldfield C and Stewart M J (1932) *J Path Bact* 35 144
- ORR J W and POLSON C J (1938) *Uterine cancer in the rabbit Amer J Cancer* 32 114 (Includes a tabular summary of previous reports with 5 interesting additions)
- Pack G T and Le Fevre R G (1930) *J Cancer Res* 14 167
- Polson C J (1927) *J Path Bact* 30 603
- Quinlan W S and Cuff J R (1940) *Arch Path* 30 393
- REICHI W (1933) *Zur Frage der Metastasierung des Uteruskrebses Z Geburts Gynak* 104 209 (A valuable review and series of reports)
- Sala A M and Stein R J (1937) *Amer J Cancer* 29 125
- Sampson J A (1904) *J Amer Med Assoc* 43 1271 and 1359
- Sampson J A (1924) *Surg Gyn Obst* 38 287
- SAMPSON, J A (1934) *Carcinoma of the tubes and ovaries secondary to carcinoma of the body of the uterus Amer J Path* 10 1 (A full and beautifully illustrated study)
- Schiller W (1928) *Arch Gynak* 133 211
- Smith F R (1941) *Amer J Obst Gyn* 41 424
- Smith E C and Elmes B G T (1934) *Ann Trop Med Parasit* 28 461
- Smith G and Pemberton F A (1934) *Surg Gyn Obst* 59 1
- Snijders E P and Straub M (1923) *Trans Far East Assoc Trop Med*, p 779
- Sorsby M (1931) *Cancer and Race* London
- MM

its first digital removal, but did not recur after its second removal by superficial curetting. Secondary growths in the vaginal walls, especially from primary carcinomas of the uterus or of the kidney (q v), must not be mistaken for primary adenocarcinomas of the vagina. Primary melanomas of the vagina are described in Chapter 58.

(7) Metastases

From carcinoma of the vaginal outlet these appear first in the inguinal lymph glands but more cranially situated growths metastasize mainly to the pelvic and lower lumbar glands.

(8) Vaginal carcinoma in animals

This disease is not uncommon in horses and cattle, and is seen occasionally in dogs (Feldman).

CARCINOMA OF THE VULVA

In their structure and behaviour, the epithelial tumours of the vulva resemble those of the skin in general, but with certain special features. By far the commonest form of growth is invasive squamous cell carcinoma, much less frequent are basal cell growths, Bowen's disease, and tumours of sweat or apocrine glands and of Bartholin's glands, which we will consider separately.

(1) Frequency

Carcinoma of the vulva is commoner than carcinoma of the vagina, but is yet a relatively rare disease. Graves and Mezer saw only 66 cases while they saw 1,668 cases of carcinoma of the cervix and 475 of the body of the uterus. Rentschler estimated the disease to occur once to every 25 cases of cervical carcinoma.

(2) Age

About half of the patients are over 60 and about one third of them are in the seventh decade. The mean age in Taussig's series was 58 and in Graves and Mezer's 60 years. Patients under 35 years of age are rare.

(3) Marital state and parity

Of 154 of Taussig's patients, 101 had borne children. 42 were nulliparous and 11 were virgin. Of Rentschler's 71 cases, 11 were nulliparous.

(4) Site

The epidermis is more frequently the site of growth than the vestibular mucous membrane. In Taussig's series 104 tumours were epidermal, 11 vestibular, 12 peri urethral, and 2 from the glans of the clitoris, while 12 arose in Bartholin's glands. Graves and Mezer classified the primary sites in their cases as labial in 39, peri urethral in 9, in the region of the clitoris in 10, perineal in 2, and in

CHAPTER 32

EPITHELIAL TUMOURS OF THE VAGINA AND VULVA

CARCINOMA OF THE VAGINA

(1) Frequency

CARCINOMA of the vagina is a rare disease comprising only about 1 per cent of carcinomas of the female genital tract. In Moench's series its frequency relative to carcinoma of the cervix was 1 to 43.

(2) Age

The mean age of Moench's 59 cases was 49 years and of Emmert's 37 cases 53 years and their youngest patients were 28 and 26 years respectively. Hoge and Benn reported a vaginal tumour in an infant of 5 months fatal at the age of 3, but their microphotograph does not support their diagnosis of 'adenocarcinoma' and the nature of the tumour remains uncertain.

(3) Marital state and parity

The number of proved recorded cases is too small to permit correlation of the frequency of the disease with the reproductive history. Moench's series included 36 married and 5 single women. 7 of Emmert's 37 patients were nulliparous.

(4) Site

More than one half of the recorded tumours have arisen on the posterior vaginal wall. Emmert stated that in 13 of his 37 cases the growths were multiple but he gave no details.

(5) Pre-cancerous lesions

No definite predisposing lesions have been recognized.

(6) Structure

With rare exceptions the tumours are squamous cell carcinomas of varying degrees of anaplasia. Of Moench's 37 microscopically examined tumours 35 were squamous celled and 2 were adenocarcinomatous, and the corresponding figures in Emmert's series were 29 and 1. Remains of Gartner's duct and endometriosis of the recto vaginal septum have both been suggested as possible origins of adenocarcinomas. Meyer (1907) was the first to describe a papillary carcinoma of Gartner's duct in the vault of the vagina and Nicholson depicted a similar growth. Strachan recorded 2 cases of adenocarcinoma of papillary type and referred to other reported instances. Spencer reported a remarkable large friable adeno papillary growth attached to the vaginal fornix by a narrow pedicle. This was removed digitally and had not recurred 24 years later. I have studied a very similar friable pedunculated growth superficially attached to the upper posterior vaginal wall in a spinster of 68 years. This recurred after

- (a) *Epidermoid carcinoma*, of the usual invasive type, and usually cornifying, is by far the commonest
- (b) *Intra epidermal carcinoma* or *Bowen's disease*, non invasive for long periods, is sometimes seen (Knight, Jeffcoate *et al*) Occasionally, as in the case depicted in Figs 262 and 263, examination of the vulval tissue removed for leucoplakia shows also the changes of Bowen's disease. Two of Knight's 6 patients with Bowen's disease had leucoplakic changes as well
- (c) *Basal cell carcinoma* is rare (Wilson)



FIG 265 —Hydradenoma of vulva from a woman of 32 years ($\times 60$)

(8) Metastasis

The inguinal lymph glands may be involved early, and are estimated by Taussig to become affected during the course of the disease in about two thirds of the cases. Inflammatory swelling of the glands may, however, be mistaken for metastases, and microscopical examination of all excised glands is important for prognosis. Remote metastases have rarely been reported.

(9) Vulval carcinoma in animals

This occurs in horses, cattle and dogs. Rudduck and I studied a squamous cell carcinoma of the perineum in a 5 year old cow and a recurrent multiple squamous cell carcinoma of the labium of a 14 year old white mare.

TUMOURS OF THE VULVAL GLANDS

(1) Tumours of Bartholin's glands

These comprise well-circumscribed benign adenomas, usually cystic and mucus secreting, and invasive carcinomas, usually glandular but sometimes

Bartholin's gland in one case. Carcinoma supervening on leucoplakia often appears at multiple sites (*see below*)

(5) Pre-cancerous lesions

Pre cancerous lesions are present in a high proportion of cases. The commonest of these is the chronic form of vulval dermatitis variously designated 'leucoplakia', 'leucoplakic vulvitis', 'kraurosis' and 'scleroderma circumscripta'.



FIG. 260—Early superficial carcinoma from near clitoris in a woman aged 65. Arrows show the limits of the cancerous area as revealed microscopically ($\times 21$).

(Taussig, Adair and Davis, Ketron and Ellis). I agree with these writers that these names do not refer to distinct diseases but merely to different appearances or stages of one disease and that this is a dangerous pre cancerous condition. Microscopic evidence of it was present in the majority of specimens of vulval carcinoma which I have examined. Of Taussig's 107 microscopically verified

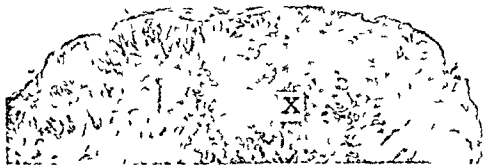


FIG. 261—Extensive superficial labial carcinoma from a woman aged 60 consisting mainly of short downgrowths from the still intact epidermis. At X there is a more deeply penetrating mass of growth ($\times 8$).

cases of epidermoid carcinoma leucoplakia was present in 74 i.e. 69 per cent. In Graves and Mezer's series the percentage was 55. Taussig estimated that one third of patients with leucoplakia will develop carcinoma while Adair and Davis considered that more than one half of them will do so. In leucoplakic

- (a) *Epidermoid carcinoma*, of the usual invasive type, and usually cornifying, is by far the commonest
- (b) *Intra epidermal carcinoma* or *Bowen's disease*, non invasive for long periods, is sometimes seen (Knight, Jeffcoate *et al*) Occasionally, as in the case depicted in Figs 262 and 263, examination of the vulval tissue removed for leucoplakia shows also the changes of Bowen's disease. Two of Knight's 6 patients with Bowen's disease had leucoplakic changes as well
- (c) *Basal cell carcinoma* is rare (Wilson)



FIG 265 —Hydradenoma of vulva from a woman of 32 years ($\times 60$)

(8) Metastasis

The inguinal lymph glands may be involved early, and are estimated by Taussig to become affected during the course of the disease in about two thirds of the cases. Inflammatory swelling of the glands may, however be mistaken for metastases, and microscopical examination of all excised glands is important for prognosis. Remote metastases have rarely been reported.

(9) Vulval carcinoma in animals

This occurs in horses, cattle and dogs. Rudduck and I studied a squamous cell carcinoma of the perineum in a 5-year old cow and a recurrent multiple squamous cell carcinoma of the labium of a 14 year old white mare.

TUMOURS OF THE VULVAL GLANDS

(1) Tumours of Bartholin's glands

These comprise well circumscribed benign adenomas, usually cystic and mucus secreting and invasive carcinomas usually glandular but sometimes

squamous celled in structure The following case affords an example of the former

Case 1—History—A woman of 60 had had a cyst of the vulva for many years. This occupied the position of Bartholin's gland and when enucleated it proved to be a well defined growth 4 centimetres in diameter composed of some solid tissue and multiple small cysts containing mucus. *Histology* (Fig 264)—The cysts were lined by cubical or columnar epithelium partly mucus secreting and in places multilayered and papillary. Other parts showed cribriform structure closely resembling that seen in mammary and salivary tumours or more disorderly adenocarcinoma like structure. The stroma and capsule were densely fibrous and partly hyaline.

Simendinger tabulated 38 recorded cases of carcinoma of Bartholin's glands. Most of these were adenocarcinomas, but others including Simendinger's case were epidermoid carcinomas. Probably no sharp separation should be made between the two types of growth, nor between these and benign tumours of somewhat atypical structure like that just described. Simendinger's review afforded no conclusive evidence that infection of Bartholin's glands predisposed them to tumour formation.

(2) Tumours of sweat and apocrine glands

These do not differ from those of other parts of the skin (see Chapter 14). The vulva is one of the commonest sites of benign hydradenoma (see Danforth, Gardner and Fig 265) and locally malignant growths of the same kind also occasionally occur here (McDonald).

REFERENCES

- Adair F L and Davis M E (1935) *Surg Gyn Obst* 61 433
 Danforth W C (1943) *Amer J Obst Gyn* 45 329
 Emmert F V (1938) *Amer J Obst Gyn* 36 1058
 Feldman W H (1932) *Neoplasms of Domesticated Animals* p 288 et seq Philadelphia
 Gardner G H (1943) *Amer J Obst Gyn* 45 331
 Graves S C and Mezer J (1942) *Amer J Obst Gyn* 43 1016
 HAUSER G (1897) Beitrag zur Histogenese des Plattenepithelkrebses und zur Lehre vom regionalen Recidiv Thiersch's *Beitr path Anat* 22 587 (Contains an excellent account of the widespread origin of vulval carcinoma.)
 Hoge R H and Bern V A (1943) *Amer J Obst Gyn* 46 286
 Jeffcoate T N A, Davie T B and Harrison C V (1944) *J Obst Gyn* 51 377
 Ketron L W and Ellis F A (1935) *Surg Gyn Obst* 61 635
 KNIGHT R van D (1943) Bowen's disease of the vulva *Amer J Obst Gyn* 46 514 (A beautifully illustrated account of 6 cases.)
 McDonald J R (1941) *Amer J Clin Path* 11 890
 Meyer R (1907) *Z Geburts Gynak* 59 234
 Moench L M (1931) *Amer J Obst Gyn* 22 837
 Nicholson G W (1923) *Gyn & Hosp Rep* 73 37
 RENTSCHLER C B (1929) Primary epithelioma of the vulva. An analysis of 71 cases, *Ann Surg* 89 709
 Simendinger E A (1939) *Surg Gyn Obst* 68 952
 Spencer H R (1923) *J Obst Gyn* 30 44
 Strachan G I (1932) *J Obst Gyn* 39 566
 TAUSSIG F J (1940) Cancer of the vulva *Amer J Obst Gyn* 40 764 (A useful account of 155 cases.)
 Taussig I J (1941) *Cancer Res* 1 901
 Wilson J M (1941) *Arch Surg* 43 101

CHAPTER 33

EPITHELIAL AND RELATED TUMOURS OF THE TESTIS AND EPIDIDYMIS

INTRODUCTION

IT WOULD be of little use to recount the confused views which were held of the nature of testicular tumours during the later part of last century when sarcomas and "endotheliomas" abounded and when many teratomas were called "chondromas", "chondro carcinomas", "rhabdomyomas", "myo chondromas", etc., according to the tissues which had been detected in them. Amongst the first to clarify the confusion were Chevassu (1906) and Nicholson (1907). Chevassu's admirable monograph clearly described and distinguished the two common forms of testicular growth, teratoma and seminoma, maintaining that the latter was carcinoma of the seminal epithelium ("*epithelioma seminal*"), and described also interstitial cell tumour and testicular adenoma. Nicholson independently showed that testicular sarcomas were relatively rare and seminal carcinomas common and that teratomas formed a single group of variable structure.

In 1911, Ewing, finding seminoma or seminoma-like tissue in some teratomas, advanced the view that seminomas, or as he called them, 'embryonal carcinomas', did not arise from the seminal epithelium but from teratomatous precursors, they were he said, 'one-sided developments of teratoma'. Ewing's view, maintained up to the last edition of his book in 1940 and still widely accepted, has caused great confusion in the classification and analysis of the properties of testicular tumours. 'Embryonal carcinoma' became, for many writers, a dumping ground for all cellular malignant growths, seminomas and teratomas alike.

Because malignant teratomas and seminomas do not differ greatly in their prognosis and treatment, clinicians found little disadvantage in this confusion of the two groups. But pathologists interested in the fundamental problems of histogenesis, found themselves in a dilemma. On the one hand, from the work of Chevassu, Nicholson, Dew, Bell, Deitermann and others it seemed clear that the origin of seminomas was from the spermatogenic epithelium. On the other hand the undoubted coexistence of seminoma with teratoma in some cases and studies of the hormonal results of the various testicular tumours, lent plausibility to Ewing's view and gave it wide popularity. Some writers e.g. Cairns, Innes, Harvey and Dawson attempted to reconcile the two conflicting views by assuming that primitive totipotent germinal cells in the seminal epithelium are the source of both seminomas and teratomas. This assumption is not very satisfying.

Some years ago, hoping to settle this difficulty to my own satisfaction I began to collect testicular tumours and study them as fully as the available material permitted. This material, on which the conclusions reached in this chapter are largely based, was the following.

characteristic in structure. The following case affords an example of the form.

Case I—Hirst—A woman of 60 had had a "cyst" of the vulva for many years. This occupied the position of Bartholin's gland, and when excised it proved to be a well-defined growth 4 centimetres in diameter composed of some solid tissue and multiple small cysts containing mucus. *Hirst* (Fig. 264)—The cysts were lined by cubical or columnar epithelium, partly mucous-secreting, and in places multilayered and papillary. Other parts showed cribriform structure closely resembling the seen in mammary and salivary tumours, or more disorderly adenocarcinoma-like structure. The stroma and capsule were densely fibrous and partly hyaline.

Simendinger tabulated 38 recorded cases of carcinoma of Bartholin's glands. Most of these were adenocarcinomas but others including Simendinger's case were epidermoid carcinomas. Probably no sharp separation should be made between the two types of growth, nor between these and benign tumours of somewhat atypical structure like that just described. Simendinger's review afforded no conclusive evidence that infection of Bartholin's glands predisposed them to tumour formation.

(2) Tumours of sweat and apocrine glands

These do not differ from those of other parts of the skin (see Chapter 14). The vulva is one of the commonest sites of benign hydradenoma (see Danforth Gardner and Fig. 265) and locally malignant growths of the same kind also occasionally occur here (McDonald).

REFERENCES

- Adair F L. and Davis, M E (1935) *Surg Gyn Obst* 61 433
 Danforth W C (1943) *Amer J Obst Gyn* 45 329
 Emmert, F V (1938) *Amer J Obst Gyn* 36 1058
 Feldman W H (1932) *Neoplasms of Domesticated Animals* p 288 et seq Philadelphia
 Gardner G H (1943) *Amer J Obst Gyn* 45 331
 Graves, S C., and Mezer J (1942) *Amer J Obst Gyn* 43 1016
 HAUSER, G (1897) *Beitrag zur Histogenese des Plattenepithelkrebses und zur Lehre vom regionalen Recidiv Thiersch's Beitr path Anat* 22 587 (Contains an excellent account of the widespread origin of vulval carcinoma.)
 Hoge R H and Benn V A (1943) *Amer J Obst Gyn* 46 286
 Jeffcoate T N A, Davie T B and Harrison C V (1944) *J Obst Gyn* 51, 377
 Ketron L W and Ellis, F A (1935) *Surg Gyn Obst* 61 635
 KNICHT R van D (1943) Bowen's disease of the vulva *Amer J Obst Gyn* 46 514
 (A beautifully illustrated account of 6 cases.)
 McDonald J R (1941) *Amer J Clin Path* 11 890
 Meyer R (1907) *Z Geburts Gynak* 59 234
 Moench L M (1931) *Amer J Obst Gyn* 22 837
 Nicholson G W (1923) *Guy's Hosp Rep* 73 37
 RENTSCHLER C B (1929) Primary epithelioma of the vulva. An analysis of 71 cases, *Ann Surg* 89 709
 Simendinger E A (1939) *Surg Gyn Obst* 68 952
 Spencer H R (1923) *J Obst Gyn* 30 44
 Strachan G I (1932) *J Obst Gyn* 39 566
 TAUSIG F J (1940) Cancer of the vulva *Amer J Obst Gyn* 40 764 (A useful account of 155 cases.)
 Taussig F J (1941) *Cancer Res* 1 901
 Wilson J M (1941) *Arch Surg* 43 101

and my own series respectively. The disease is rare before the age of 30 and almost unknown under 20 years. Bell (1938) has recorded the development of seminoma in a boy of 16 years with bilateral incomplete descent of the testes. The findings in my youngest patient are worthy of special note.

Case 1—History—A married man aged 27 years, father of 3 children, had both testes in the inguinal position: the right testis lay in the inguinal canal and could not be drawn into the scrotum; the left testis, which felt abnormally firm and nodular, lay at the external ring and was accompanied by an easily reducible inguinal hernia. Left orchidectomy



FIG. 266—*Case 1*. Large lymphoid follicle in stroma of seminoma ($\times 60$)

and repair of the hernia were performed. *Examination of the testis* showed it to measure $4.5 \times 3 \times 3$ centimetres and serial thin slices showed it to contain at least 6 separate areas of white growth separated by testicular tissue: this was verified in micro-sections of the entire organ. *Histology*—Typical seminoma with unusually abundant lymphoid tissue in many places bulkier than the seminomatous tissue and forming many large follicles with germinal centres (Fig. 266). No teratomatous elements were found in any of the growths. Intervening testicular tissue showed extreme tubular atrophy and fibrosis and many large groups of interstitial cells.

(b) *The duration of tumours*

This is very variable. In some cases they grow and disseminate quickly; in others enlargement of the testis has been noticed for 5 or 10 years or longer prior to removal (references by Gordon Taylor and Till). Removal of some of these slowly growing tumours of long duration has been followed by permanent recovery, but the prognosis is bad in cases in which a previously slow growth has shown more rapid recent enlargement.

(c) *Incomplete descent of the testis*

This has long been recognized as predisposing to the development of tumours both seminomas and teratomas (Rea, Gordon Taylor, Gilbert and Hamilton

From man

Tumours showing seminoma only	-	-	-	-	21 cases
Teratomas of the testis	-	-	-	-	15 ,
Teratoma of the epididymis only	-	-	-	-	1 „
Combined seminoma and teratoma	-	-	-	-	5 ,
' Chorion epithelioma	-	-	-	-	4 ,
Probable rete carcinomas	-	-	-	-	2 ,
Multiple tubular adenomas of testis	-	-	-	-	1 ,
Interstitial cell tumour	-	-	-	-	1
Total	-	-	-	-	50 cases

From animals

Interstitial cell tumours in dogs	-	-	-	-	16 cases
Seminomas in dogs	-	-	-	-	7 ,
Sertoli cell or rete tumours in dogs	-	-	-	-	4 „
Teratomas of the testis in horses	-	-	-	-	5 ,
Total	-	-	-	-	32 cases

All of the human specimens all of the equine teratomas, and most of the other animal specimens were very fully studied microscopically usually by many blocks from thin serial slabs of the tumours with the deliberate intention of discovering all available evidence regarding histogenesis and especially regarding the possible relationships of seminoma and teratoma. In many of the human specimens including all 5 of combined seminoma and teratoma complete topographical reconstruction of the growths was attempted in the manner indicated in my paper on teratomas in 1935.

It may be as well to state at once my main conclusions namely (a) that seminoma undoubtedly arises from the seminiferous epithelium and not from teratomatous elements (b) that cellular undifferentiated teratomatous epithelium has often been mis identified as seminoma or embryonal carcinoma (c) that the occasional combination of true seminoma with teratoma results from coexistence of the two types of growth a coexistence which though not due to histogenetic relationship is not wholly fortuitous and (d) that 'chorion epithelioma' is not a distinctive type of growth and is not chorionic but is only a form assumed by haemorrhagic necrotic cellular tumours of other kinds usually teratomas.

SEMINOMA SEMINAL CARCINOMA OR SPERMATOCYTOMA

(1) Incidence and causation

(a) Age incidence

All adequate series from Chevassu's onwards show that true seminomas appear on an average more than a decade later than teratomas. The mean age of patients at the time of operation is early in the fifth decade e.g. 43 45 40 40 and 43 years in Nicholson's Bell's Deitermann's Gordon Taylor and Till's

doctor On palpation doctor thought there might be a small nodular area in testis and because of this and patient's anxiety he performed orchidectomy. Incision of testis verified presence of a small well defined rounded slightly lobulated white tumour in upper pole. *Histology*—Serial sections of the tumour showed it to be 9 millimetres in main diameter and to consist throughout of typical seminoma with no sign of teratomatous elements

(g) Trauma

Injury has often been blamed as a cause of seminomas and other testicular growths but from critical study of cases in which this is supposed to have happened it is clear that in most instances the trauma did no more than attract attention to a testis already diseased, possibly aggravating it in some

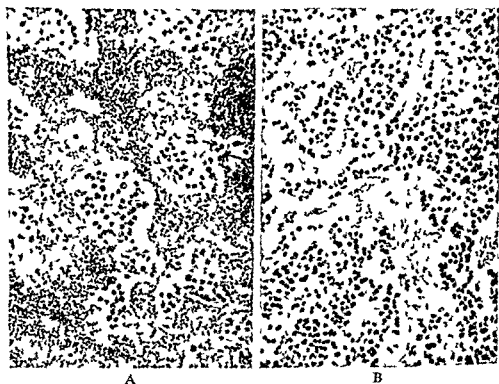


FIG 267—Typical appearances of seminoma as seen in formalin fixed paraffin embedded tissue. A with abundant B with scanty lymphoid stroma. ($\times 120$)

(h) Infections

Infections of the testis also are of very doubtful causative significance. Tuberculous epididymo-orchitis has occasionally been reported as accompanying testicular tumours (e.g. in 3 of Rea's cases), and of course a history of previous mumps is given by a proportion of the patients.

(2) Structure

(a) The characteristic structure

Most seminomas are closely similar to one another in structure and are easy to recognize at a glance and each tumour usually shows remarkable structural

and see also Bell's case and my Case I above) According to Gilbert and Hamilton ectopia is present in 11 per cent of cases of testicular tumour, a proportion 48 times greater than can be accounted for by chance if a tumour develops in a patient with unilateral ectopia, it is in the ectopic organ in almost all cases, and in men with bilateral ectopia if one testis becomes cancerous, then the other testis will also become cancerous in 25 per cent of cases, a risk 32 times greater than obtains in patients with scrotal testes Ectopia is not necessarily the direct cause of tumour formation it is more probable that it is only one expression of gonadal or more general endocrine anomaly predisposing to tumour formation in the gonadal tissues

(d) *Bilateral seminomas*

Bilateral growths are seen occasionally (Pearson Hamilton and Gilbert) The two testes may suffer nearly simultaneously as in Pearson's case or a period of many months or years may intervene between the appearance of the two tumours Hamilton and Gilbert from a review of the literature, concluded that in a man with testicular cancer the likelihood of cancer arising in the second testis is hundreds of times greater than the chance expectation and that the risk is greatest in patients with imperfect descent Teratomas as well as seminomas may be bilateral

(e) *Multiple seminomas in one testis*

Multiple growths in one testis as in my Case I are seldom demonstrable in human specimens, but are frequently seen in dogs (see below)

(f) *Familial incidence*

Testicular tumours including seminomas have occasionally been seen in two or more close relatives Champlin described the occurrence of testicular tumours in identical twins one died at 24 years of age of a testicular sarcoma with intracranial metastases and at the age of 31 years the other developed a seminoma which was removed and had not recurred 3 years later Raven reported a seminoma in a man of 38, whose brother had had an inoperable testicular tumour (not examined microscopically) at the age of 18 Lownes and Leberman described two brothers one of whom had a spermatocytoma removed at the age of 32 years but died later from pulmonary metastases and the other had a testicular teratoma removed at the age of 53 years the photographs are poor and the nature of the second tumour is uncertain The following case was remarkable not only for the family history of testicular disease but also for the small size of the tumour

Case II (Dr G C Burston's case) —Family history—Paternal grandfather died at the age of 30 years from bilateral ulcerated cancer of the testes father was killed in an accident and had no known disease of the testes elder brother at age of 31 developed tumour of testis diagnosed by a pathologist as teratoma metastases in retroperitoneal lymph glands and liver were seen at laparotomy and he died later *Patient's history*—When aged 15 he was operated on for undescended right testis this was successfully placed in scrotum but remained only about half normal size At age of 38 he developed aching pain in groin became apprehensive because of family history and consulted his

in the tubules (Fig 268) This relationship has been interpreted by Ewing and others as due merely to tumour invasion of, and extension within, the tubules. The appearances seen, however, cannot be explained in this way, but point clearly to progressive neoplastic change in the seminal epithelium. The seminomas of dogs (*see below*) often show transitions from normal to neoplastic tissue in the spermatid tubules, and afford particularly conclusive evidence of the true origin of these tumours

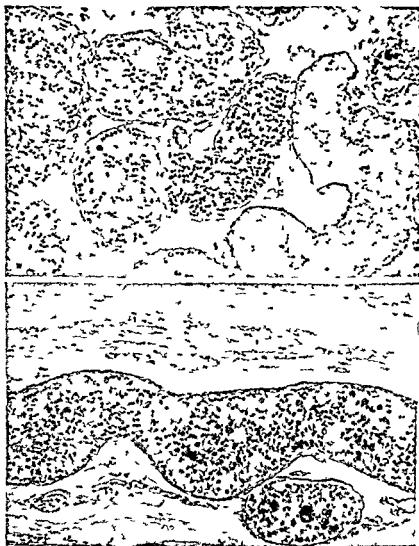


FIG 268 —Intra tubular growth around the margins of a large seminoma ($\times 80$)

(3) Are teratomatous tissues found in seminomas?

Keeping for separate consideration those tumours in which the coexistence of seminoma and teratoma is plain to the naked eye or on cursory microscopical study, we are left with those common seminomas in which on gross examination the tumour tissue appears of more or less uniform structure throughout and preliminary representative micro sections show seminoma only. If Ewing's view

uniformity in all parts, save where this is altered by degenerative changes. The characteristic appearances are depicted in Figs 267 273 278 and 280. The tumours consist of well or ill defined clumps of large rounded polyhedral cells of average diameter about 15 or 20 μ but sometimes even 30 μ or more, with distinct cell boundaries each with a single large spherical nucleus and a rim of pale poorly staining cytoplasm devoid of any distinctive structures. The close similarity of the cells to spermatocytes in many tumours noted particularly by Bell is sometimes very striking and in itself points strongly to the spermatogenic origin of the growths. Mitotic figures vary greatly in number, according to the rate of growth of the tumours. In rapidly growing tumours they are often very plentiful and conspicuous.

In a personal communication Dr Leila Hawksley has drawn my attention to the great differences in appearance of the cells of seminomas according to the fixative used. The plump spherical shape of the cells is much better preserved by Bouin's Orth's or Zenker's fluid than by plain formalin or formalin salt solutions in which shrinkage and distortion often take place. Dr Hawksley also informs me that alcohol fixed seminoma cells show a high glycogen content.

The stroma consists of strands of connective tissue and blood vessels characteristically accompanied by a variable number of lymphocytes. These may be scanty and found in only parts of the tumour, or they may be very numerous forming broad lymphoid areas alternating with masses of tumour cells. Rarely this lymphoid tissue is as abundant as the tumour parenchyma and forms plentiful large follicles as well as diffuse areas as in Case I. The relative proportions of tumour parenchyma and lymphoid stroma though varying greatly from tumour to tumour are usually fairly constant throughout each tumour. Oedema of the stroma is sometimes prominent.

(b) *Less usual structural variants*

These are of three main kinds. (i) Parts of the tumours sometimes show compact masses of large irregularly polygonal or elongated cells with denser cytoplasm giving more distinctly epithelial appearances. Growths in which this type of structure is prominent have often been designated carcinomas as distinct from seminomas but more complete study will show that the distinction is not valid for one tumour may contain areas of both structural types with transitions between them. (ii) Diffuse anaplastic seminomas are occasionally difficult to recognize histologically and may be mistaken for sarcomas. (iii) Near areas of necrosis or haemorrhage seminoma cells may become atypical showing enlargement and fusion. Rarely multinucleated masses resembling the syncytium of the so called chorion epitheliomas may be produced in this way.

(c) *Relationships to the seminal tubules*

In specimens in which residual testicular tissue is still present the relationship of the growth to this is often of great interest. I can abundantly confirm the findings of Hartmann *et al* Bell and others that individual seminal tubules occupied by tumour are often to be found marginal to the main growths and that all transitions can be traced between normal spermatogenic tissue and tumour tissue.

(4) Extension and metastasis of seminomas

(a) *Extra testicular extension*

Direct spread to the epididymis and cord is frequent. Discrete nodules of growth may appear along the cord above the main growth, presumably by local embolic spread in veins or lymphatics. Extension to the skin, ulceration and fungation are of course seldom seen nowadays.



FIG. 269 —Intra tubular multifocal seminoma in a fox terrier aged 14 years ($\times 40$)

(b) *Metastasis to lymph glands*

This is the major risk. The first glands to be affected are those of the upper lumbar groups, about the level of origin of the spermatic arteries. In a high proportion of fatal cases tumour deposits are present here, and in deciding on operability of a testicular tumour, and in the follow up of patients already operated on, careful palpation for possible retroperitoneal metastases is the most important part of the clinical examination. Other lymph glands become involved secondarily to the disease in the lumbar group or following extension of inoperable growths to surrounding tissues.

(c) *Metastasis by the blood stream*

Haemic dissemination occurs later and less frequently from seminoma than from malignant teratoma. The prognosis of seminoma is correspondingly better than that of teratoma, and as Gordon-Taylor and Till have rightly insisted, far too pessimistic an outlook has prevailed regarding testicular neoplasms. Since

were correct, we should certainly expect that thorough serial study of these tumours especially small ones would often reveal residues of the teratomas from which they are supposed to have sprung. But such residues are *not* found in the ordinary seminomas. Bell, Deitermann and Innes *et al* all failed to discover any signs of heterotopic tissues in their seminomas. In my own series of 21 seminomas I deliberately searched for such tissues with special thoroughness usually in many sections from thin serial slabs of the entire tumours but found no sign of teratomatous elements.

Ewing admitted that teratomatous elements could not be found in most seminomas but supposed this to be due to complete suppression of slowly growing and scanty structures in the original focus. Yet grossly obvious specimens of combined seminoma and teratoma are *not* unusual (*see below*) and if these are taken to support Ewing's hypothesis we should surely discover even more frequent microscopic examples of the combination. This however is not the case, and this very discrepancy argues strongly against the hypothesis.

Again Ewing's assertion that scanty teratomatous elements are soon overgrown and destroyed by the rapidly advancing carcinoma is very dubious. On the contrary study of malignant teratomas shows plainly that islands of cartilage, squamous epithelial cysts and other well differentiated structures are *not* readily overgrown and destroyed by more malignant anaplastic components of the growths and moreover many seminomas are *not* rapidly advancing destructive tumours.

Ewing's Case I on which he largely based his concept of obliteration of teratomatous tissues by seminoma contains in fact no evidence relevant to this question. The tumour showed two rather distinct portions one of which proved to be seminoma and the other teratoma the latter being sharply circumscribed from the testis. This teratomatous part was progressing rapidly by the growth of several types of carcinoma and capable of yielding eventually one of the pure types of carcinoma testis. If this tumor had been allowed to grow to the size of a hen's egg it would have been regarded as adenocarcinoma or chorioma in one portion and diffuse carcinoma or alveolar sarcoma in the others. This is pure assumption. All that the tumour actually showed was two rather distinct portions one seminomatous the other teratomatous.

The occasional presence of small islands of cartilage in seminomas has often been cited in support of Ewing's hypothesis. The only recorded instance of this which I have read is that of Leroux and Hufnagel who found associated with a seminoma an area of cystic tubules and some nodules of cartilage. These were interpreted not as teratomatous but as due to obstructive dilatation of the excretory ducts of the testis and metaplastic chondrification of the stroma.

Briefly then the facts are these. The ordinary seminoma of grossly homogeneous naked eye appearance has a homogeneous microscopic structure and thorough serial examination even of small or slowly growing tumours shows no signs of teratomatous tissues. The concept of submergence and obliteration of a pre-existing teratoma by seminomatous growth lacks substantial evidence and is wholly imaginary.

tumour No II, on which he laid such stress, was 9 centimetres in diameter and that it was not examined topographically

Briefly then, embryonic epithelial growth in teratomas can be, and has been, mistaken for seminoma or "embryonal carcinoma" (used synonymously for seminoma) But, this source of confusion can and should be avoided by careful study of the material When, however, tissue structurally indistinguishable from seminoma is found in a teratoma, it may still be some teratomatous component merely mimicking seminoma, or it may be true seminoma invading the teratoma from without These possibilities must always be carefully weighed before concluding that true seminoma has arisen within a teratoma

Age incidence—In all adequate series of cases the mean age of patients with teratomas is about 10 years younger than that of patients with seminomas, e.g. 28 in Chevassus and in Gordon Taylor and Till's series and 32 in mine A further striking difference is that, while seminoma rarely, if ever, occurs in childhood and adolescence, teratomas often do so and are sometimes known to have been present at birth Thus, in Chevassus's series there were 5 specimens of teratoma from infants but no case of seminoma under 20 years of age The fact that, although teratomas, some of them malignant, are not unusual in childhood and adolescence, seminomas are practically unknown during this period strengthens the case against Ewing's hypothesis

Teratoma testis in animals—The only mammal I believe, in which testicular teratomas have been observed is the horse (Willis, Rudduck and Willis, Innes) These tumours appear to be commoner than their human counterparts, are present in young animals, are usually benign and highly differentiated and may be multiple and bilateral Seminomas, which occur relatively rarely in the horse, are not associated with teratomas The spontaneous and experimental testicular teratomas of birds are discussed in Chapter 61

COEXISTENT SEMINOMA AND TERATOMA

(1) Previous reports

In addition to those tumours in which teratoma and seminoma or seminoma-like growth have been found intimately associated, there are several reports of cases in which the two have coexisted as distinct and separate tumours or in which their relationships have been such as to suggest that they had originally been separate

Lecene (1907) briefly recorded a testicular tumour from a man 40 years of age which showed both teratoma and seminoma No topographical study was made, but in many pieces examined the two forms of growth were everywhere separated by a zone of connective tissue and nowhere infiltrated one another In a second specimen reported by Lecene (1909) the testis of a man of 25 years contained two quite separate growths one a seminoma and the other a cystic teratoma the latter encapsulated by a fibrous zone

many seminomas grow slowly and metastasize late many permanent cures can be effected by prompt surgery Seminomatous metastases are commonest in the lungs and liver and are rare in other parts

(5) Seminomas in animals

Seminomas clearly the counterparts of those in man are very common in old dogs They have been well described by Schlotthauer *et al* McDonald *et al*, Innes and Huggins and Pazos with whose findings Rudduck's and mine on specimens from 7 dogs are in substantial agreement Like human seminomas the canine ones are not infrequently bilateral and they appear to affect undescended testes with disproportionate frequency Early tumours are often demonstrably



FIG 270 Intra tubular seminoma in a Pomeranian dog aged 13 years ($\times 100$)

multiple intra tubular seminoma *in situ* is often conspicuous (Figs 269-270) and the progressive origin of the growths from spermatogenic cells of the seminal tubules is often clear and unmistakable The careful study of a few good specimens of canine seminomas should soon convince any competent histopathologist both that these tumours are the same as human seminomas and that they arise from the spermatogenic epithelium—spermatogonia or spermatocytes A still further point in evidence against the hypothesis that seminomas are of teratomatous origin is the fact that while canine seminomas are common teratomas of the dog's testis are extremely rare if indeed they ever occur as far as I know there are no recorded examples Canine seminomas are much less malignant than their human counterparts growing slowly and rarely metastasizing However Fig 271 depicts invasion of the tunica albuginea and Rudduck and I saw also a large seminoma in an 8 year old setter with metastases in the lumbar lymph glands and liver

(2) Personally studied cases

I have examined the following 5 cases in which seminoma and teratoma coexisted topographical study showing certainly or almost certainly that the two kinds of growth were distinct in 4 cases, and that they may originally have been distinct in the remaining case

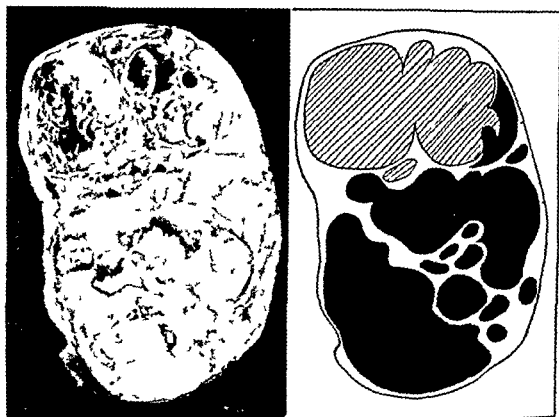


FIG 272—Case III A vertical section with key diagram showing seminoma black and teratoma hatched (Slightly reduced)

Case III (Mr H C Trumble's case)—History—A man of 23 years had noticed swelling of one testis for several months orchidectomy was performed Palpable retroperitoneal masses were noticed about 1 year later these diminished following X ray treatment, but later recurred and patient died 3 years later at age of 27 years *Naked eye examination* showed an ovoid lobulated growth $8 \times 5 \times 5$ centimetres surrounded on most aspects by a compressed layer of residual testis A series of thin vertical slices showed that the upper third of the tumour consisted of polycystic growth characteristic of teratoma and its lower two thirds of homogeneous solid white and partly necrotic growth on the mediastinal side the two areas had visible residual testis intervening between them but on the opposite side they were closely contiguous but still well demarcated This demarcation was apparent in all slices one of which is depicted in Fig 272 The slices were all cut into numbered blocks from which micro-sections were prepared *Microscopical examination* confirmed that the upper third of the tumour was malignant teratoma and the lower two-thirds typical seminoma The teratomatous tissue comprised a variety of well differentiated glandular structures disorderly adenocarcinoma like tissue keratinized nests of squamous stratified epithelium smooth muscle,

In Ewing's Case I already referred to the testis of a man of 38 years contained a tumour $2 \times 1\frac{1}{4} \times 1$ centimetres composed of two rather distinct portions one seminomatous and the other which was sharply circumscribed from the testis teratomatous and containing chorionatous elements. In Ewing's Case II the tumour from a man of 61 years included both a highly differentiated teratomatous growth and a large area of seminoma the latter judging from Ewing's diagram enveloped the former peripherally but was fairly distinct from it but no details are given regarding the exact relationships of the two kinds of growth.

A brief note records that Menetrier *et al* saw two tumours in the one testis a seminoma and a chorioma separated by testicular tissue.

Another specimen of coexisting but distinct seminoma and teratoma in a man of 36 years was fully described by Hartmann *et al*. The seminoma, typical in structure and showing clear evidence of its derivation from the testicular tubules occupied the upper pole of the testis. A chorioma occupied the mediastinal area and epididymis and was separated from the seminoma by a zone of connective tissue. It showed typical chorion-epitheliomatous structure but with transitions to papillary epithelial formations. The authors regarded the seminoma as having arisen in the testis independently of but consecutive to a pre-existing embryoma, the latter becoming predominantly chorionatous.

Roussy and Huguenin described a tumour from a man of 20 years. One area of the growth was typical seminoma and another was a teratoma with cysts and papillary tubular epithelial structures regarded as Wolffian. No topographical details are given but the two parts of the growth were said to be distinct.

McClure *et al* found in the testis of a man of 29 years a well delimited teratoma separated from the surrounding testicular tissue by a thin but definite capsule of fibrous tissue along with an area of spermatocytoma in residual testicular tissue at the upper pole of the organ. The appearance seen in further slices of the bisected testicle suggesting that the tumour passes as a band from the upper to the lower pole. The authors described the tumour as showing a seminoma in addition to the malignant teratoma.

Nicod reported a tumour from a man of 26 years in which both seminomatous and carcinomatous parts were present infiltrating each other in places. Their topography was not fully determined but Nicod interpreted them as having been distinct tumours which had coalesced.

In the testis of a man of 27 years McDonald and Broders found two distinct tumours which though in continuity in places were for the most part separated by normal testicular tissue or by a capsule. One tumour was a teratoma and the other a seminoma. Detailed topographical study was not undertaken. McDonald and Broders also mentioned a specimen reported by Mercier and Bourque in which three separate tumours—a teratoma, a seminoma and a chorion-epithelioma—are said to have been present. Peyron reported having seen examples of coexisting seminoma and teratoma.

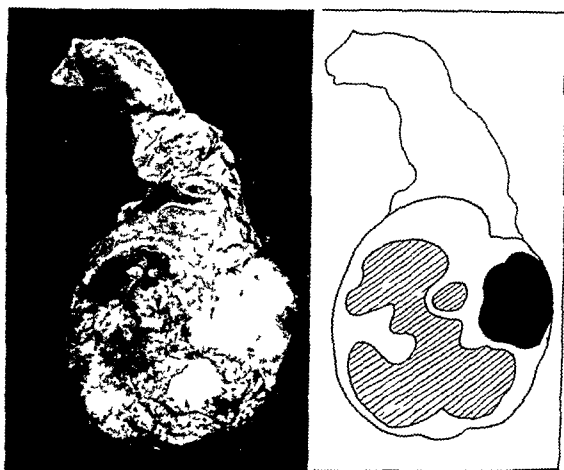
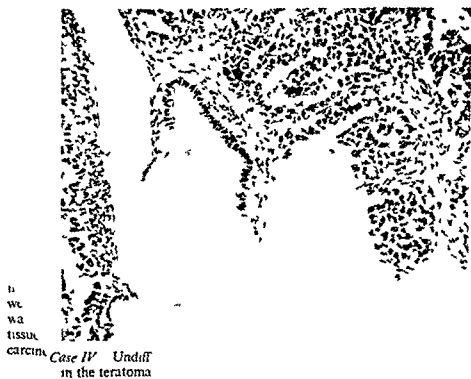


FIG. 274 — *Case IV* A vertical section with key diagram showing seminoma black and teratoma hatched (Slightly reduced)



and immature spindle-celled mesenchyme. The disorderly adenocarcinoma like epithelium was plentiful and in places formed irregular meshworks or diffuse sheets and its large polyhedral cells showed many mitotic figures. This tissue resembled that of Figs 275 and 276 and bore a superficial resemblance to seminoma in places but closer study showed that it could everywhere be distinguished from the typical seminoma in the lower two thirds of the testis. Sections of the zone between the teratomatous and seminomatous areas showed these to be well separated in most parts by a band of residual testis and a thick fibrous layer but that on the outer side of the testis the two kinds of tumour became closely contiguous and a tongue of seminoma intervened between the outer aspect of the teratoma and the tunica albuginea. However no seminomatous tissue was found within the limits of the teratomatous growth. Calcified spherules were present in residual atrophic seminal tubules included in the seminoma (Fig. 273).

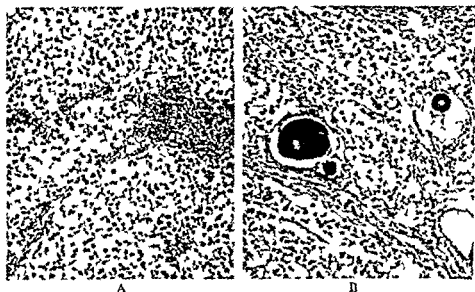


FIG. 273.—Case III. Seminoma of typical structure in A with calcified intra tubular spherules in B ($\times 115$).

Case IV—History—A man of 28 years had noticed enlargement of left testis for 3 months. orchidectomy was performed. his final fate is not known. *Naked eye examination* showed a lobulated tumour 7 centimetres in main diameter surrounded by a zone of residual testis of maximal width 1 centimetre at the upper pole. One well-defined lobule of growth 2 centimetres in diameter in the mediastinal region consisted of homogeneous white tissue the remainder of mottled grey brown and haemorrhagic growth (Fig. 274). The whole tumour was cut into vertical slices and then into 26 numbered blocks from which micro-sections were prepared. *Histology* (Figs 275 and 276)—The white lobule of growth had the typical structure of seminoma and was everywhere distinct from the teratomatous remainder though closely contiguous with it in part. The teratoma consisted largely of disorderly poorly differentiated adenocarcinoma like growth like that of Case III and of a small patch of better differentiated tissues comprising some small cysts lined by squamous stratified epithelium or by papillated columnar epithelium and glands of alimentary type accompanied by lymphoid tissue and cellular spindle-celled mesenchymal tissue. No seminomatous tissue was found within the teratoma some of the least differentiated parts of which however might have been mistaken for seminoma on superficial examination (Fig. 276).

later *Naked eye examination*—Testis measured $4 \times 4 \times 3$ centimetres and was largely replaced by growth in its upper third this consisted of lobules of homogeneous white tissue in its lower two-thirds of irregularly cystic tissue the two areas appearing fairly distinct (Fig 277) *Histology* (Fig 278)—The white area of growth is typical seminoma the cystic part is malignant teratoma containing cysts lined by goblet-celled alimentary epithelium or by columnar or cuboidal epithelium of nondescript type cornified cell nests and spaces lined by epidermis-like epithelium plentiful poorly differentiated papillary or retiform epithelial tissue smooth muscle around some of the cysts small nodules of cartilage and much cellular spindle-celled mesenchyme Vertical sections at several different planes show that the two kinds of growth are everywhere separated by a thick zone of fibrous tissue except at one place (marked X in Fig 277B) where the seminoma has slightly invaded the periphery of the teratoma over a small area

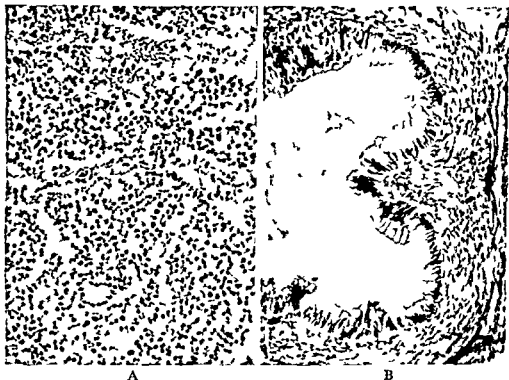


FIG 278—Case V A from seminoma B from teratoma ($\times 120$)

Case VI—History—A man of 34 years had noticed swelling of right testis for 9 months orchidectomy was performed final result not known *Naked eye examination*—An ovoid tumour $14 \times 9 \times 8$ centimetres was enclosed within the tunica albuginea with only a thin rim of compressed residual testis on outer surface It was composed of mottled white and degenerated solid tissue with a few well defined small cysts near upper pole The whole tumour was cut into vertical slices and then into 64 numbered blocks from which micro-sections were prepared *Histology*—Most of the tumour is clearly teratomatous consisting of much disorderly adenocarcinoma like growth along with a variety of better differentiated glandular structures mainly of mucus secreting columnar-celled alimentary type cornified cell nests and scanty smooth muscle and small nodules of cartilage Extensive necrosis has taken place in many parts of the teratomatous tissues and near the necrotic areas the poorly differentiated epithelial tissue shows swelling and fusion of the cells to produce chorion-epithelioma like appearances At parts of the periphery there is a layer of typical seminoma measuring up to 1 centimetre in thickness in some places restricted to the peripheral zone of residual testis and distinctly separate from the teratoma in other places mingled with it Where seminoma mingles with the undifferentiated epithelial component of the teratoma it is difficult to distinguish them No seminomatous tissue is present in the central parts of the growth it is restricted to the periphery

*Case V (from Dr Leila M Hawksley formerly pathologist to the Cancer Hospital London)—History—*A man of 27 years had noticed rapid enlargement of left testis for 2 weeks orchidectomy was performed a palpable upper abdominal mass was treated by deep X ray irradiation and patient was well and no mass palpable 6 months

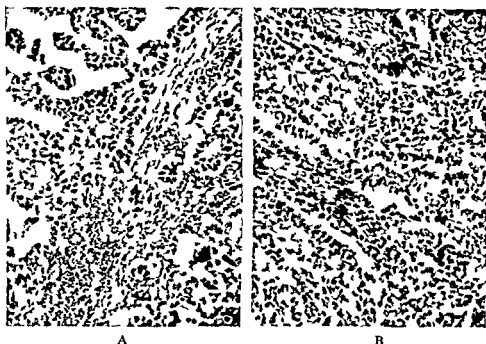


FIG 276—*Case IV* Undifferentiated teratomatous epithelium in A accompanied by lymphocytes in B compressed and diffuse ($\times 110$)

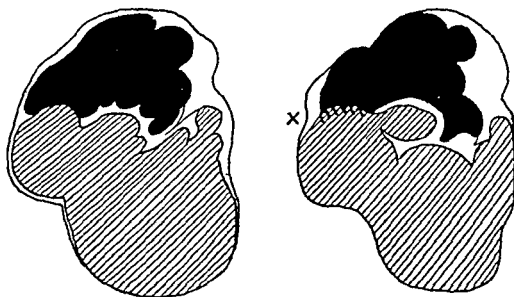


FIG 277—*Case I* key diagrams of two vertical sections showing seminoma in black and teratoma hatched (Actual size)

of benign structure, in all of the others the teratomas (or "chorion epitheliomas") were of the malignant type usual to the testis. The mean age of the cases, excluding these two, was 29 years, a figure identical with that for malignant testicular teratomas generally.

I know of no example of associated seminoma and teratoma in an animal. Seminomas are common in old dogs, but canine testicular teratomas are unknown. Teratomas are rather common in horses, but seminomas are rather rare and have not been reported in association with the former.

(4) Is the coexistence of seminoma and teratoma fortuitous?

In my opinion the facts enable us to answer *no* to this question. All testicular tumours are rare, and therefore the purely fortuitous coexistence of tumours of two distinct kinds in one testis would be excessively rare. Yet, as we have seen, the coexistence is not very unusual, and it would certainly be discovered more frequently if examination of excised testicular tumours were more thorough. The fact that no less than 5 cases of coexistence occurred in my series of 50 tumours, most of which were unselected, indicates far more than a mere chance association.

In speculating on the relationship of the two growths, one fact seems clear: the teratoma precedes the seminoma. This is evident, not only from the general principle that mammalian teratomas take origin in early stages of development (see Chapter 61), but also from the descriptions of the tumours in the cases just reviewed. In several of these (e.g. those of Lecene, McClure *et al.* McDonald and Broders, and my Case VII) the teratoma is described or depicted as a well circumscribed encapsulated mass, and in others, including Ewing's second case and my Case VII, the maturity of some or all of the teratomatous tissues points to their relative quiescence and long duration. The seminoma on the contrary is usually of the actively growing type with many mitoses and has often clearly been the component responsible for recent rapid enlargement of the testis. However, while there is little doubt that the development of the seminoma follows on that of the teratoma and not vice versa, it is also noteworthy that in many cases the teratomatous component also shows evidence of recent active growth and malignancy.

What then is the possible relationship between a pre-existing teratoma and a supervening but separate seminoma? Only a speculative answer can yet be given. We know that a developmentally abnormal testis, such as an imperfectly descended one, is strongly predisposed to seminoma. Now, a testis containing a teratoma from early life is also a developmentally abnormal one. Perhaps, then, it also for some similar but as yet undefined reason, is predisposed to later seminoma. Whether this hypothetical predisposition may be due to some primary disturbance of metabolism or endocrine control of the abnormal organ, or to diffusible products of the teratoma affecting the testicular tissues, or merely to obstructive effects resulting from the mere presence of the teratoma, we cannot say. Whatever the explanation, it at least seems clear that the coexistence of seminoma and teratoma in one testis is not purely fortuitous, but that a

Case VII (from Dr Leila M Hawksley formerly pathologist to the Cancer Hospital London)—*History*—A man aged 54 years had had enlarged right testis for 13 years growing larger during last 3 years orchidectomy was performed patient remained well 1 year later *Gross structure*—Testis and epididymis were both enlarged forming mass 6 centimetres in main diameter the testis contained a lobulated tumour 4 centimetres in diameter composed of white tissue with some areas of yellow necrosis, and the globus major of the epididymis contained a separate well defined growth 2.5 centimetres in diameter composed of masses of bone and cartilage cystic spaces and solid soft tissues *Histology*—Tumour in testis is a typical seminoma composed of unusually large cells with many mitoses and showing many areas of necrosis near which the cells show giant and syncytial forms reminiscent of choriocarcinoma Abundant residual testicular tissue shows advanced tubular atrophy interstitial fibrosis and many large clumps of interstitial cells Tumour in epididymis is a well circumscribed encapsulated benign cystic teratoma composed of fully differentiated quiescent bone cartilage adipose tissue cysts lined partly by ciliated pseudo stratified epithelium and partly by simple cuboidal or flat epithelium abundant smooth muscle fibres around the cysts a few striated muscle fibres and occasional patches of neuroglial tissue

(3) Discussion of foregoing cases

Of my 5 cases, the coexisting seminoma and teratoma were shown certainly to be distinct and separate growths in 2 (IV and VII) they had almost certainly been separate but showed close contiguity or very early localized infiltration in 2 cases (III and V) and they were not separate but showed extensive infiltration in Case VI In the 10 cases reviewed although detailed topographical studies were not undertaken it is either clear or very probable that the growths were distinct and separate in 5 namely those of Lecene (second case) Menetrier *et al* Hartmann *et al* McClure *et al* and McDonald and Broders the relationships are less certain but the tumours may well have been separate in 4 namely Lecene's first case Ewing's two cases and Roussy and Huguenin's case while mutual infiltration was present in Nicod's case Thus of the total 15 cases the tumours were either demonstrably separate or there was clear evidence that they had been separate in 9, in the two cases in which considerable infiltrative mingling of the two tissues was present (Nicod's and my Case VI) the distribution of the tissues suggested invasive coalescence of formerly distinct growths and in the remaining 4 cases the relationships are uncertain None of the cases showed what they should have shown if Ewing's hypothesis had been correct any evidence of histogenetic relationship between the teratomatous and seminomatous tissues

The ages of the 15 patients with combined tumours are noteworthy They ranged from 20 to 61 years and averaged 33 years Thus the combined tumours tend to occur about the same ages as malignant teratomas of the testis and decidedly earlier than uncomplicated seminomas but like seminomas none of them has occurred in childhood or early adolescence In the two oldest patients in the series—Ewing's second case and my Case VII, aged 61 and 54 years respectively—the teratomatous growths were of highly differentiated benign type and I suggest that in both cases benign quiescent teratomas had long been present unnoticed until independent seminoma supervened In Case VII the old benign teratoma in the epididymis was widely separated from the seminoma in the testis but in Ewing's case the seminoma soon enveloped the old teratomatous elements in the testis These two cases are the only ones of the 15 with teratomas

tissue discovered is the well known cellular undifferentiated epithelium in its various forms—papillary, villous, syncytial, etc. The structure produced may closely simulate that of true gestational chorion epithelioma, but so also may



FIG. 280—Typical seminoma from a man of 45 years ($\times 80$)



FIG. 281—Chorion epithelioma like syncytial structure in the same tumour as Fig. 280 ($\times 80$)

teratoma containing human testis is predisposed to the later development of seminoma in the remaining testicular tissue. When this happens the teratoma often but not always, shows signs of active growth and malignancy also.

CHORION EPITHELIOMA OF THE TESTIS

My series contains 4 tumours the haemorrhagic necrotic naked eye appearances and microscopical structure of which conformed with those of chorion epithelioma and in which no other definitely teratomatous elements were discovered (Fig 279). In the better preserved areas of these growths however the supposed chorionic epithelium was identical with the undifferentiated papillary and reticular epithelial structures to which I have already referred as a frequent component of malignant testicular teratoma (Figs 275-276). Further, small haemorrhagic and necrotic foci in otherwise well preserved malignant teratomas



FIG 279 — Chorion-epithelioma of testis of a man of 22 years ($\times 80$)

show an identical structure and the distinction between such teratomas and chorion epitheliomas is the purely arbitrary one of how much haemorrhagic necrotic change the tumours show. The observations of Nicholson, Sternberg, Schmeel, Mönckeberg, Reckendorf, Handfield Jones, Ahlstrom, Ross, McDonald and many others show how frequently chorion-epithelioma of the testis is demonstrably teratomatous. Many of these writers also have traced the relationship of the chorion-epithelioma like tissue to other rapidly growing components of the teratomas. I agree with the following conclusion from the paper by Ross. The 'chorion-epitheliomatous' tissue arises by the metamorphosis of undifferentiated cells which also give rise to carcinoma and to teratomatous structures. These cells are in fact pluripotential.

A chorion-epithelioma is merely a rapidly growing teratoma in which haemorrhage and necrosis are abundant and the predominant or only viable

later *Necropsy*—The testis was largely replaced by an ovoid slightly lobulated firm tumour 8 centimetres in diameter composed of white tissue with patchy yellow degeneration invading also the central part of the epididymis. Lumbar lymph glands were much enlarged by masses of soft growth with gross invasion of inferior vena cava and left renal vein. Cisterna chyli was invested and there were tumour deposits in left supraclavicular lymph glands. Lungs and liver contained many rounded metastases. *Histology*—All parts of growths showed disorderly papillary adenocarcinoma (Fig 282) no areas like seminoma and no teratomatous tissues were found on extensive search of primary tumour.

Case IX—A second specimen of unknown history consisted of a large pyriform growth 20 centimetres in vertical measurement invading the cord cranially and scrotal skin over its lower pole. Its structure throughout was similar to that of Case VIII but showed also the metaplastic formation of plentiful pale squamous cells from parts of the papillary growth.



FIG 282—*Case VIII* Papillary carcinoma of rete testis $\times 80$

The unusual multiple tumours in the following case are of interest, because they appear clearly to have arisen from the excretory ducts, and because they bear on the histogenesis of the multiple testicular adenomas.

Case X—History—A man 59 years of age, believed to have prostatic carcinoma (not proved microscopically) was treated by stilboestrol and double orchidectomy. *Gross examination* of testes on section revealed in one testis a single rounded tumour 5 millimetres in diameter in the mediastinal part and in the other testis 3 similar nodules (i) 4 millimetres in diameter in the mediastinum (ii) 7 millimetres in diameter near the opposite side of the testis and (iii) 2 millimetres in diameter near the centre of the organ. *Histology* (Fig 283)—Many sections of all 4 tumours showed similar structure consisting of well differentiated tubules lined by simple cubical or low columnar epithelium with large darkly staining nuclei and slightly basophil cytoplasm. Haemorrhage had taken place into the lumina of some of the tubules. Mitotic figures were plentiful and the tumour elements had infiltrated amidst the surrounding testicular tubules. In structure and staining properties the tumour tubules closely resembled those of the straight and rete tubules seen in the same sections and in spite of the distance of one of the tumours from the mediastinum it is concluded that this was their origin.

highly cellular carcinomas of other regions e.g. of the liver or stomach. Syncytial change in rapidly growing epithelial tumours does not denote specific chorionic characters, but is merely a form of growth—or perhaps of unhealth—of cells in proximity to necrosis or haemorrhage.

The rapid invasive growth of tumours of this kind and their ready extension into blood vessels explain their speedy dissemination by the blood stream to the lungs and other organs. Metastases may produce the first symptoms of disease such as haemoptysis or signs of cerebral tumour (Ahlstrom, Ross, Duncan). In a remarkable group of cases bulky chorion epithelioma like metastases develop from small structurally benign looking testicular teratomas (Prym, Symeonidis, Craver and Stewart).

No chorion epitheliomas of the testis in animals have been recorded. This is not surprising since teratomas of the testis have not been described in any animal except the horse in which they are always or nearly always of the benign quiescent type.

Can anaplastic seminomas assume chorion epithelioma like structure? All the tumours which I have seen in which much of this structure was present have consisted of embryonic epithelium like that of Figs 275 and 276 with or without more differentiated teratomatous tissues and I suspect that many of those who believe they have seen chorion epithelioma like structure related to seminoma or embryonal carcinoma have misidentified cellular areas of undifferentiated teratomatous epithelium. However G. W. Nicholson informs me that he studied an unusually haemorrhagic typical well differentiated seminoma with great syncytia round the haemorrhages and Case VII above and the specimen depicted in Figs 280 and 281 exemplified the same feature.

TUMOURS OF SERTOLI CELLS AND OF THE EXCRETORY DUCTS OF THE TESTIS

The excretory ducts of the testis comprise the straight tubules, rete, efferent tubules, epididymis and ductus deferens. Epithelial tumours usually malignant of all of these are very rare and of those arising within the testis particularly careful study is essential in order to distinguish them from teratomas with predominant glandular epithelial structures. It is probable also that no sharp distinction can or should be drawn between Sertoli-cell tumours and tumours of the excretory ducts. Sertoli cells and excretory ducts are histogenetically allied non-spermatic epithelia.

(1) Intra-testicular tumours of the excretory ducts or Sertoli cells

(a) Rete and allied carcinomas

I have examined two testicular tumours which I believe to be carcinomas of the straight rete or efferent tubules.

Case I III—History.—A man of 31 years who had had gonorrhoea 4 years previously complained of painful enlargement of right testis for 3 months. Wassermann reaction was found strongly positive. Diagnosis of syphilitic orchitis was made and course of N.A.B. injections given. Swelling persisted and increased and 3 months later patient was admitted to hospital with pain in chest and dyspnoea and skiagrams showed multiple large rounded shadows in both lung fields. Wassermann now negative. He died 1 month

Gordon-Taylor and Till depicted a solid spheroidal cell carcinoma of the epididymis. The common cystic dilatations of parts of the epididymis should of course, not be called "adenoma" or "cystadenoma".

INTERSTITIAL CELL TUMOURS

Marked hyperplasia of Leydig's interstitial cells is of course frequent in imperfectly descended testes or in organs undergoing atrophic changes from tumours or other causes. True neoplasms of the interstitial cells, however, are rare in the human testis. Good examples and references are given by Rowlands and Nicholson (1929), Sutherland Stewart *et al*, Braun, Warren and Olshausen, Bonser and Hawksley, and Neeve and Marsh. The tumours are usually well circumscribed, brown or orange in colour, and consist of masses of closely packed polyhedral or elongated cells with granular or vacuolated cytoplasm, which often shows faint brownish pigmentation, and in which special stains show the presence

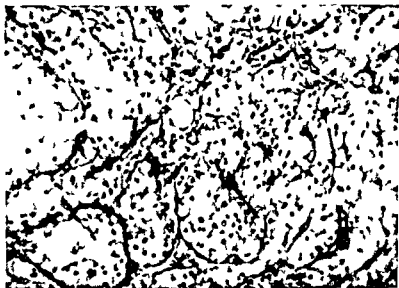


FIG 284.—Interstitial-cell tumour with vacuolated cells from a kelpie aged 6 years. Sudan III stained frozen sections showed plentiful fat droplets in cells ($\times 150$)

of fine or large droplets of fat, most of which is isotropic but some anisotropic (Figs 284, 285). Most of the tumours are benign, growing slowly and not producing metastases, but metastasis has been reported occasionally. The tumours occur most frequently in adults between 30 and 50 years old. When they have developed in young children, there has been precocious sexual development (Sutherland, Stewart *et al*).

Tumours closely similar to the human ones occur spontaneously in animals, especially in dogs (Schlotthauer *et al*, Innes, Huggins and Pazos). Rudduck and I found interstitial cell tumours in 16 dogs, the tumours being single in 10 and multiple or bilateral in 6 animals (Figs 284, 285). No sharp distinction can be made between nodular hyperplasia and early neoplasia of the Leydig cells. The

(b) Tubular adenomas

These occur rarely in man as small multiple benign tumours in pseudo hermaphrodites or cryptorchids (Chevassu, Ide, Kruckmann) and structurally similar tumours occur occasionally in the ovary (q v). There seems little doubt that these tumours usually arise from the non spermatic component of the seminal tubules, the Sertoli cells and that they are the counterparts of the much larger and more common Sertoli cell tumours of dogs (Schlotthauer *et al* Innes Huggins and Pazos). Rudduck and I studied 5 tumours of this kind from 4 dogs, bilateral growths being found in one animal. Case X above is of interest in showing points of resemblance both to carcinomas of the excretory ducts and multiple adenomas of the testis. It suggests that no sharp line of separation need be drawn between excretory duct epithelium and its tumours on the one hand and Sertoli cells and their tumours on the other. In my opinion this view is supported also by study of the canine tumours the structure of some of which is compatible with an origin from either Sertoli cells or rete ducts.

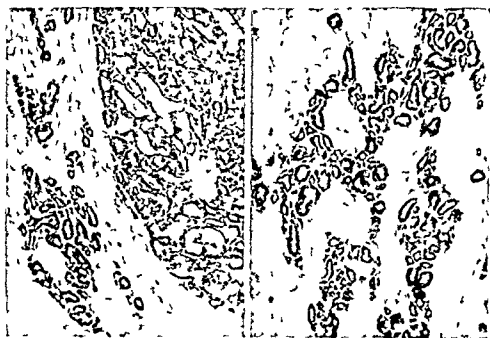


FIG. 293—Case X. Multiple tubular adenomas. ($\times 80$)

(2) Extra testicular tumours of the excretory ducts

Epithelial tumours of the epididymis and ductus deferens are very rare. Rowlands and Nicholson (1909) described a squamous cell carcinoma of the epididymis and Thompson (1936) reported and collected examples of adenocarcinoma of this organ. While the figure of Thompson's Case 33 depicts undoubtedly adenocarcinoma this diagnosis is dubious in his Fig. 9 which shows a growth exactly like that which I have regarded as a benign lymphangioma (Fig. 347).

by the disappearance of hormonal disturbances following removal of the tumour in some cases, and their reappearance with the growth of recurrent tumour or metastases. Interstitial cell tumours constitute a special case in which precocious puberty may be attributed to the direct effects of androgen from the secreting tumour cells. (ii) The tumours, by producing testicular atrophy or other secondary effects on the gonadal tissues, may disturb the balance of sex hormones. (iii) Some victims of testicular tumour may already have had some previous endocrine imbalance, as in pseudo hermaphrodites or cryptorchids. Of these three possibilities the first seems the most probable. But before speculating further, we need further careful hormonal assays from cases of testicular tumours and correlation of the findings with careful histological studies of the responsible tumours. To this end we particularly need clear ideas regarding the histogenesis of the tumours unclouded by misconceptions about the origin of seminomas and about the use of the capacious pigeon hole labelled "embryonal carcinoma".

SUMMARY OF THE NATURE AND CLASSIFICATION OF TESTICULAR TUMOURS

The evidence presented in this chapter warrants the following grouping and nomenclature of the epithelial and allied tumours of the testis

(1) Seminomas

These are, as Chevasu held, seminal carcinomas. They arise from the spermatocytic cells of the tubules, and are appropriately called also *spermatocytomas*. They are unrelated histogenetically to teratomas, but not infrequently arise in testes already containing teratomas.

(2) Teratomas

Malignant or benign, these are the counterparts of the ovarian and other teratomas. They frequently contain much cellular undifferentiated epithelial tissue, which on the one hand by superficially mimicking seminoma may promote confusion of the two classes of tumour under the designation "embryonal carcinoma" and on the other hand may undergo haemorrhagic changes and assume a chorion epithelioma like structure. Most "*chorion-epitheliomas*" of the testis are only rapidly growing haemorrhagic teratomas, a few of them may be haemorrhagic seminomas.

(3) Carcinomas or adenomas of the excretory ducts

These may be either (a) intra testicular, arising from the epithelium of the straight tubules, rete or efferent tubules, or (b) extra testicular, arising in the epididymis. Allied to, and perhaps not to be sharply separated from tumours of the intra testicular excretory ducts, are *Sertoli cell tumours* or *tubular adenomas*.

(4) Interstitial-cell tumours

These closely resemble their parent tissue, the cells of Leydig.

REFERENCES

- AHLSTROM C. G. (1931) Zur Kenntnis des Chorionepithelioms beim Manne. *Acta Path. Microbiol. Scand.* 8: 213. (A good critical review)

experimental production of interstitial cell tumours in mice by oestrogens is described in Chapter 4

HORMONAL RESULTS OF TESTICULAR TUMOURS

Tumours of the testis and their metastases are often associated with hormonal disturbances, which though of great interest, are still far from fully understood. These results include increased urinary excretion of gonadotrophins, sometimes sufficient to give a positive Aschheim Zondek test of intensity as great as that in normal pregnancy or in true chorion epithelioma and hyperplasia and secretory activity of the male breast. Instances of these results have been reported by Handfield Jones Prym, Sas Herdrich *et al*, Mackenzie and Ratner Storzjohann Symeonidis Duncan and Ferguson *et al*. The fact that in many such cases the tumours have consisted wholly or partly of chorion epithelioma like growth has been advanced in support of Schlagenhauser's view that the testicular growths of this kind are indeed chorionic in nature and essentially the same as the true gestational chorion epitheliomas and this view appeared to be supported by the very high titre of the Aschheim Zondek test in some of the cases.

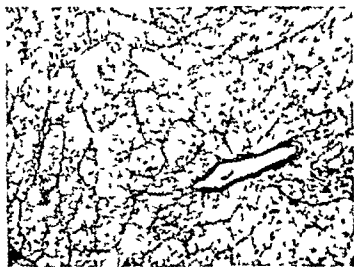


FIG. 285.—Interstitial-cell tumour with compressed clear-celled structure from a dog. Sudan III stained frozen sections showed much fat in the cells ($\times 100$).

That the problem is a more complex one, however, is shown by the following facts: (a) Seminomas and testicular teratomas devoid of chorion-epithelioma like tissue can produce similar though usually not so intense endocrine disturbances (Zondek, Ferguson *et al*). (b) Gynaecomastia occurs in many conditions other than testicular tumours including testicular atrophy, adrenal cortical tumours, pituitary tumours or hepatic disease (Herzenberg, Busch, Ahlström, Bergonzi, Weber).

We may speculate on the several possible ways in which testicular tumours may be associated with endocrine disturbances: (i) The tumour itself may produce hormones or substances capable of disturbing hormonal balance; this is supported

- Ross J M (1932) *J Path Bact* 35 563
- Roussy F and Huguenin R (1924) *Ann Anat path* 1, 505
- Rowlands R P and Nicholson G W (1909) *Lancet* 1 304
- Rowlands R P and Nicholson G W (1929) *Guy's Hosp Rep* 79, 401
- Rudduck H B and Willis R A (1943) *J Path Bact*, 55 165
- Sas L (1930) *Arch klin Chir*, 161 682
- Schlagenhauser F (1902) *Wien klin Wschr* 5 571 604
- SCHLOTTHAUER, C F, McDONALD J R, and BOLLMANN, J L (1938) Testicular tumors in dogs *J Urol* 40 539 (An excellent account)
- Schmeel W (1909) *Frankfurt Z Path* 2 232
- Sternberg C (1904) *Verh Dtsch path Ges* 7 105
- Stewart C A Bell E T, and Roehlke A B (1936) *Amer J Cancer*, 26, 144
- Storjohann K R (1932) *Frankfurt Z Path* 43 80
- Sutherland D M (1933) *Brit J Surg* 20 343
- Symeonidis A (1934) *Beitr path Anat* 94 370
- THOMPSON, G J (1936) Tumors of the spermatic cord epididymis and testicular tunics, *Surg Gyn Obst* 62 712 (A useful review of this heterogeneous group)
- Warren S and Olshausen K W (1943) *Amer J Path* 19 307
- Weber F P (1929) *Proc Roy Soc Med* 22 415
- Weber F P (1946) *Rare Diseases* p 92 London
- Willis R A (1934) *Brit J Exp Path* 15 234
- Willis R A (1935) *J Path Bact*, 40, 1
- Willis R A (1938) *Med J Austral* 1 287
- Willis R A (1938) *J Path Bact* 46 198
- Zondek B (1931) *Amer J Cancer* 15 1833 (abst)

- BELL F G (1926) Tumours of the testicle *Brit J Surg* 13 7 282 (An excellent well illustrated account)
- Bell J G Y (1938) *Proc Roy Soc Med* 31 610
- Bergonzi M (1934) *Virchows Arch* 293 697
- Bonser G M and Hawksley L M (1943) *J Path Bact* 55 295
- Braun H (1939) *Virchows Arch* 304 106
- Busch J P (1927) *Dtsch med Wschr* 53 323
- Cairns H W B (1926) *Lancet* i 845
- Champlin H W (1930) *J Amer Med Assoc* 95 96
- Champy C and Lavedan J P (1939) *Bull Assoc franç Cancer* 28 503
- CHEVASSU M (1906) *Tumeurs du testicule* Paris (A classical and excellent monograph)
- Craver L F and Stewart F W (1936) *J Amer Med Assoc* 106 1802
- Deitermann J H (1937) *Frankfurt Z Path* 50 231
- Dew H R (1925) *Malignant Disease of the Testicle* London
- Duncan C A (1938) *Med J Austral* ii 867
- Ewing J (1911) *Surg Gyn Obst* 12 230
- Ferguson R S Downes H R Ellis E and Nicholson M E (1931) *Amer J Cancer* 15 835
- Ferguson R S (1933) *Amer J Cancer* 18 269
- Gilbert J B and Hamilton J B (1940) *Surg Gyn Obst* 71 731
- GORDON TAYLOR G and TILL A S (1938) On malignant disease of the testicle *Brit J Urol* 10 1 (A valuable clinical survey)
- Hamilton J B and Gilbert J B (1942) *Cancer Res* 2 125
- HANDFIELD JONES R M (1926) Chorionic carcinoma in the testicle *Brit J Surg* 13 606 (A useful review)
- Hartmann Menetrier *et al* (1922) *Bull Assoc franç Cancer* 11 319
- Heidrich L Fels E and Mathias E (1930) *Beitr klin Chir* 150 349
- Herzenberg H (1927) *Virchows Arch* 263 781
- Huggins C and Pazos R (1945) *Amer J Path* 21 299
- Ide N (1933) *Beitr path Anat* 91 241
- INNES J R M (1942) Neoplastic disease of the testis in animals *J Path Bact* 54 485 (A well illustrated personal study and review)
- Innes J R M (1943) *Brit J Surg* 31 157
- Innes J R M Harvey W F and Dawson E K (1938) *Edinb Med J* 45 36
- Kruckmann I (1937) *Virchows Arch* 298 619
- Lecène P (1907 and 1909) *Bull Soc Anat* 1907 9 678 1909 11 349
- Leroux R and Hufnagel (1927) *Ann Anat path* 4 786
- Lownes J B and Lebermann P (1939) *Urol Cutan Rev* 43 205
- McClure J Sanguinetti H H and Carlton C H (1932) *Brit J Urol* 4 217
- McDonald J R and Broders A C (1941) *Amer J Clin Path* 11 138
- McDonald J R Schlotthauer C F and Bollman J L (1938) *Surg* 3 904
- McDonald S (1938) *Amer J Cancer* 34 1
- Mackenzie D W and Ratner M (1931) *Surg Gyn Obst* 52 336
- Menetrier Peyron and Isch Wall (1922) *Presse med* p 538
- MÖNCKEBERG J G (1907) Über Syncytiumhaltige Hodentumoren *Virchows Arch* 190 381 (An excellent critical review)
- Neeve R H and Marsh F (1944) *J Path Bact* 56 575
- NICHOLSON C W (1907) New growths of the testicle *Gus s Hosp Rep* 61 249 (A classical paper which along with Chevassu's monograph inaugurated modern concepts of histogenesis)
- Nicod J L (1933) *Bull Assoc franç Cancer* 22 86
- Pearson E L (1932) *J Urol* 28 353
- Peyron A (1939) *C R Acad Sci* 208 1946
- Prym P (1925) *Dtsch med Wschr* 51 1149
- Prym P (1927) *Virchows Arch* 265 239
- Prym P (1930) *Beitr path Anat* 85 703
- Prym P (1930) *Zbl allg Path* 49 98
- Raven R W (1934) *Lancet* ii 870
- Rea C E (1931) *Amer J Cancer* 15 2646
- Reckendorf W (1921) *Virchows Arch* 234 460

(3) Age incidence

Prostatic carcinoma is notable as occurring later in life than any other form of malignant disease, appearing on an average a decade later than carcinomas in the aggregate. About three quarters of clinical cases are in the seventh and eighth decades, the peak of the age distribution curve is towards the end of the seventh decade, and most of the deaths from this disease take place in the eighth decade (Bumpus-Gordon). The mean age of my 40 necropsy cases was 72 years. The disease is very rare before the age of 40.

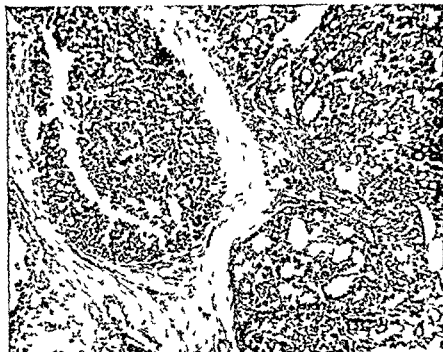


FIG. 286.—Prostatic adenocarcinoma from an Alsatian dog 9 years old (Case 1 of Rudduck and Willis) ($\times 80$)

(4) Causation

The view that *benign hyperplasia* is a significant pre-cancerous lesion and that carcinoma often supervenes on it is difficult either to prove or disprove. This view is based mainly on the closely similar age incidence of the two diseases, the probability—still however, unproved—that both are related to endocrine disturbances (Moore), and the frequent coexistence of hyperplasia with carcinoma. The last argument, however, carries little weight, for most prostates from middle-aged or old men show some degree of nodular hyperplasia. Hence, while it is quite possible, even probable, that hyperplasia and neoplasia of the prostate are related, it remains for future research to prove and define the relationship.

There is no substantial evidence to support the view that *inflammatory diseases* predispose to carcinoma of the prostate. The occasional coexistence of venereal infections, tuberculosis or calculi is no more than coincidental.

(5) Prostatic carcinoma in animals

Adenocarcinoma is not unusual in elderly dogs (Feldman, Rudduck and Willis, Schlotthauer and Millar, and see Fig. 286) but has only rarely been

CHAPTER 34

CARCINOMA OF THE PROSTATE

FREQUENCY AGE INCIDENCE CAUSATION

(1) Frequency

BECAUSE prostatic cancer often escapes clinical diagnosis its real frequency cannot be estimated from registered mortality figures. The disease probably accounts at present for about one tenth of male deaths from cancer e.g. in the United States of America in 1938 11.5 per cent of registered deaths from cancer were attributed to prostatic cancer (Go don). Most necropsy series record between 5 and 15 per cent of fatal carcinomas in males as prostatic, e.g. 40 of 635 cases (6 per cent) in my series in Table V, Chapter 5.

Several workers by thorough examination of prostates surgically removed or obtained *post mortem* have claimed to show that small symptomless growths structurally carcinomatous are present in a surprisingly high proportion of men past middle age e.g. 13 per cent of men over 60 years of age (Muir) 18 per cent of men of average age 69 years (Gaynor) 14 per cent of men over 40 (Rich) 18 per cent of men over 40 (Moore) 17 per cent of men over 50 (Kahler) and 46 per cent of men over 50 (Baron and Angrist). The magnitudes of and especially the great discrepancies between these estimates raise doubts regarding the histological criteria for the diagnosis of carcinoma adopted by some of these workers. Baron and Angrist's conclusion that nearly one half of the male population over 50 years of age is affected by prostatic cancer seems incredible. While all experienced pathologists will agree that routine microscopical examination will disclose undoubted early carcinoma in a proportion of men in whom it has not been suspected clinically or on naked eye examination of the prostate the exact proportion is still I think very uncertain. The histological distinction between benign hyperplasia and carcinoma is not always easy to make and there may well be room for much difference of opinion regarding the diagnosis of carcinoma in many routinely examined prostates. However it would not be a matter for great surprise if it were proved that say 5 or 10 per cent of men in the seventh and eighth decades had unsuspected prostatic cancers. The seeming discrepancy between such a finding and the clinical frequency of the disease would readily be accounted for by the well known fact that prostatic cancer often grows slowly and symptomlessly and by the high mortality from other causes in the elderly.

(2) Race

Comparisons of the incidence of prostatic cancer in different races are quite unreliable. The factor of differences of age composition—still largely unknown for many non European peoples—is of particular significance in this disease which is chiefly one of old age. The fact that prostatic cancer has only occasionally been recorded in the Chinese (Moore) is of little significance. Cooray however records that 50 of 1815 carcinoma biopsies in Ceylon were from the prostate and American records include many cases in Negroes.

hyperplastic or inflamed prostatic tissue, and care must be taken not to mistake these for carcinoma



FIG 288 —Well differentiated prostatic adenocarcinoma ($\times 150$)

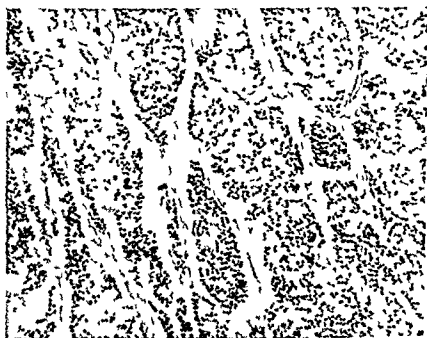


FIG 289 —Imperfectly differentiated prostatic adenocarcinoma ($\times 120$)

The stromal reactions evoked by prostatic carcinoma These deserve special note. Familiar to all clinicians and pathologists is the osteoplasia induced by metastatic growths in bones, leading to ivory condensation of parts of the affected

recorded in other mammals. Engle and Stout saw multifocal prostatic carcinoma without metastases in an old monkey. By means of benzpyrene Moore and Melchionna produced squamous cell carcinomas but no adenocarcinomas in the rat's prostate. Recently however Horning obtained transplantable adenocarcinomas in inbred mice, from subcutaneous prostatic grafts wrapped round methylcholanthrene crystals.

STRUCTURE

The following structural variants are seen in prostatic carcinomas. Several or all of them may be seen in one tumour.

(a) *Adenocarcinoma* consisting of distinct tubules or acini is by far the commonest type of growth. Almost all tumours show glandular structure in parts, though the degree of differentiation varies. Many tumours consist largely

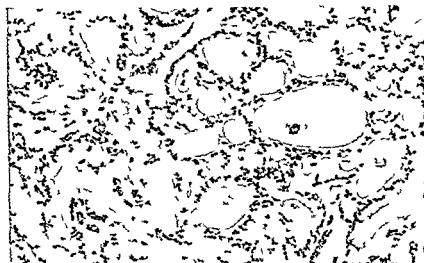


FIG. 287 —A metastasis of well differentiated prostatic adenocarcinoma in a cervical lymph gland. the primary growth had been symptomless and unsuspected. ($\times 120$)

of well differentiated small acini so characteristic that their prostatic origin is readily detected or suspected by the experienced microscopist (Figs. 287-289). Other tumours show tubular, cystic or papillary structure not diagnostic of a prostatic origin. Mucoid carcinoma as in the case described by Klissurow is rare.

(b) *Spheroidal celled carcinoma simplex* appears in the scirrhous or desmoplastic form less commonly in the cellular anaplastic form. As Cappell has shown diffuse carcinoma may simulate and has no doubt often been misdiagnosed as sarcoma or a tumour consisting partly of well differentiated and partly of diffuse carcinoma may be called carcinoma sarcoma.

(c) *Squamous metaplasia* in parts of an adenocarcinoma is rare. Nicholson (1923) referred to several cases. Kahler saw squamous celled carcinoma in 6 of 195 cases. Areas of squamous metaplasia are sometimes present in simple

cures Many untreated cases of this disease progress slowly and with symptomatic remissions, and in some treated cases, even those initially responding favourably the growths have nevertheless progressed and metastases have developed later Hormonal therapy cannot yet be regarded as effecting more than temporary suppression of some tumours

SPREAD AND METASTASIS

(1) Local spread

The extension of carcinoma to the capsule of the organ and to the periprostatic tissues takes place by the usual routes, namely tissue spaces, lymphatics and small veins Warren *et al* and Kahler have stressed the frequency of permeation of perineural lymphatics but in my opinion have given it undue prominence The hypothesis that this is a usual route by which secondary deposits reach the lumbar vertebrae and pelvic bones is not in accord with the distribution of skeletal metastases disclosed by thorough necropsies (*see below*) Gross invasion of the bladder, rectal wall and other pelvic soft tissues occurs in advanced cases Invasion of the erectile tissues of the penis may cause priapism (Fronz and Alyea, Guibal and Pavic)

(2) Metastases in lymph glands

Lymph glands are affected, sometimes very extensively, in a high proportion of fatal cases, e.g. in 77 per cent of Muir's cases, the groups of glands involved being the internal iliac, external iliac, lumbar, inguinal, thoracic and supraclavicular, in that order of frequency Lymph nodal deposits were present in 26 of my 40 necropsies i.e. 65 per cent Lundsgaard reported a case in which large cervical growths were the first signs of a small symptomless primary growth A specimen which I examined consisted of a mass of growth 6 centimetres in diameter in the axillary lymph glands, excised as probable Hodgkin's disease, microscopically, this showed the typical structure of small acinar prostatic adenocarcinoma, and rectal examination then revealed hard nodular enlargement of the prostate

(3) Blood-borne metastases

(a) In viscera

Blood borne metastases are present in the viscera in about 40 per cent of fatal cases, the organs most frequently affected being the lungs, liver and adrenals

(b) In bones

Skeletal metastases develop in a high proportion of cases—from 30 to 70 per cent in various reported series The higher estimates are probably nearest the truth, the frequency with which these metastases are recorded depending of course upon the thoroughness of the radiographic or necropsy examination of the skeleton Skeletal metastases not infrequently produce the first or main symptoms of disease (Willis, 1934), persistent 'lumbago', 'sciatica' or other 'rheumatic' pains, or obscure bone tumours or pathological fractures in elderly men should always excite suspicion of possible cancer of the prostate So also should

bones and to irregular osteophytes (*see below*) The fact that prostatic cancer in bone evokes osteoplasia almost regularly and with much greater frequency than any other kind of tumour strongly suggests that this reaction is due to some specific diffusible substance liberated from the tumour cells Occasionally, metaplastic formation of bone occurs in the connective tissue stroma of primary prostatic cancer or in metastases in soft tissue as in Nicholson's case (1924 Fig 77) and Schmorl's case referred to in Chapter 8 This special bone evoking property of prostatic carcinoma may well be related to its phosphatase activity, it is possible that the secretion of acid phosphatase by prostatic epithelium and of alkaline phosphatase by osteoblasts may together be concerned in the osteoplastic reaction

METABOLIC PECULIARITIES OF PROSTATIC CARCINOMA

(1) Secretion of phosphatase

Prostatic carcinoma shares with normal prostatic epithelium the power of secreting large amounts of acid phosphatase (Gutman *et al* Watkinson *et al* Haddow) Kutscher and co-workers first discovered that normal adult prostatic tissue is very rich in a phosphatase with optimal activity at pH 5.0 The Gutmans then showed that this enzyme was plentiful also in cancerous prostatic epithelium in both primary and secondary growths and later that patients with metastases in bones usually showed markedly increased amounts of acid phosphatase in the blood serum In cases of non-prostatic carcinoma with skeletal metastases and in most cases of Paget's disease, raised values of serum acid phosphatase were seldom found so that this test may sometimes be of value in the differential diagnosis of sclerosing lesions of bone of doubtful nature The amount of alkaline phosphatase in the serum in various bone diseases fluctuates independently of that of the acid phosphatase, it depends not on secretory activity of epithelial cells, but on osteoblastic activity either in reactive states of bone or in osteogenic tumours (q.v.)

(2) Hormonal control

It has long been recognized that castration causes atrophic changes in the prostate—indeed John Hunter was aware of this—and beneficial results have been obtained by castration in cases of benign, and more recently of cancerous enlargement of the prostate The discovery that administration of oestrogens also benefited some patients with carcinoma of the prostate has led to formulation of the general principle that the growth of prostatic cancer is encouraged by androgens and inhibited by oestrogens Progressive histological studies and also estimations of the level of serum acid phosphatase following castration or oestrogen treatment support this view (Watkinson *et al*, Huggins and Hodges Schenken *et al* Fergusson and Pagel) It is now apparent that the characteristic epithelia of the normal prostate and of the benign and (some) malignant tumours of the gland have much in common as regards their phosphatase content their dependence upon androgenic activity and their reaction to orchidectomy or the administration of oestrogens (Haddow) Although striking alleviation has been obtained in many cases of prostatic cancer by castration or hormonal treatment it is still too soon to conclude that these measures may effect permanent

common sites of metastases from other tumours, and doubtless for the same reason namely that they are large bones containing red marrow. Radiologists, having their attention focused on these bones because of the prevalent teaching regarding their mode of involvement from prostatic cancer, and also finding them a convenient field in which to search for metastatic lesions, naturally discover such lesions here more often than they discover them elsewhere, and so obtain a false impression of their relative frequency.



FIG 291 —Osteoplastic vertebral metastasis of the tumour shown in Fig 288 ($\times 150$)

The route of dissemination of metastases in the skeleton is of course bound up with their distribution. My necropsy experience typified in Fig 292, leads me to conclude that this takes place mainly by the usual routes, namely by invasion of veins or major lymphatics from the prostatic growth or its lymph nodal metastases, embolic dissemination to the lungs, and thence to the bones via the systemic blood stream. Batson has advanced the interesting hypothesis that the rich vertebral venous plexus is the usual route of dissemination of prostatic and other growths to the axial skeleton. While recognizing that this route may well be an important auxiliary one after establishment of growths in the vertebral region and of collateral channels of flow, following tumour invasion of large pelvic or vertebral veins, there is no reason to suppose that it supersedes the well established route via the lungs. Batson, like many other workers, regards the not infrequent freedom of the lungs from growths in cases with metastases elsewhere as a 'paradox'. But, of course, adequate microscopic study of such lungs will often confirm Schmidt's finding of arrested tumour emboli in pulmonary arterioles, and will show that the 'paradox' is largely imaginary (see Chapter 10). In several cases of disseminated prostatic cancer without grossly obvious metastases in the lungs I have searched for and found minute metastases or arrested tumour emboli in the lungs. It is quite probable however, that a prostatic growth or its

radiographic discovery of multiple osteoplastic lesions in bones with rare exceptions osteoplastic metastatic carcinoma in men is prostatic in origin (Figs 290 291) Radiographically extensive osteoplastic carcinosis can be mistaken for Paget's disease The metastases of prostatic carcinoma in bone have been well described by von Recklinghausen Kaufmann Fischer Defoy Axhausen Joll Purckhauer and Zemgulyš

The distribution of the metastases in the skeleton deserves special comment It is often asserted mainly on radiographic evidence that the pelvis lumbar vertebrae and upper ends of the femora are affected with disproportionate frequency whence it is concluded that these bones are usually reached by direct extension of the growth from the prostate *via* lymphatics or other channels

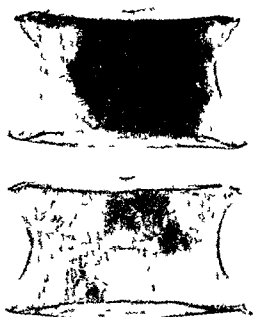


FIG 290—Skiagram of two lumbar vertebrae containing osteoplastic metastases of prostatic carcinoma

This assumption is more than doubtful Careful necropsy work shows that early metastases of prostatic carcinoma in bones are often well circumscribed rounded masses with a scattered distribution very similar to that of metastases from other primary tumours Fig 292 depicts the distribution of metastases in the vertebrae in 4 cases of prostatic carcinoma in which thorough necropsy section of these bones was undertaken These show scattered distributions of the growths with no evidence of a centrifugal relationship to the primary growth—distributions which might equally well have been found with carcinomas of the breast or stomach or thyroid It is of course true that the lumbar vertebrae and pelvic bones are common sites of metastases from prostatic cancer just as they are

the pelvis and lumbar vertebrae This opinion was based on the frequent finding of cancerous permeation of these lymphatics in the periprostatic tissues in 7 cases with metastases in these bones It must be noted, however, that 4 of the 7 cases had visible metastases in the lungs, that there is no record of microscopical search of the lungs for tumour emboli in the other 3 cases, that only the pelvis and lumbar vertebrae were subjected to special examination and there was no necropsy study of the distribution of tumours in other parts of the skeleton, and that the authors admit that while perineural permeation was common in the periprostatic tissues "very little evidence was found of involvement of nerves or of their lymphatics extending towards the bony pelvis"

CARCINOMA OF THE SEMINAL VESICLES

Authentic examples of this disease are very rare Clinically, they are either regarded as carcinomas of the prostate or they cause errors of diagnosis by their metastases Trachsler reviewed previous records, and reported a case in which vertebral metastases led to a diagnosis of primary spinal disease Junghanns reported a case of 'sarcoma'—possibly anaplastic carcinoma—of the seminal vesicles with cerebral metastases which simulated primary brain tumour

REFERENCES

- Axhausen G (1909) *Virchows Arch* 195 358
 Baron E and Angrist A (1941) *Arch Path* 32 787
 Batson O V (1940) *Ann Surg* 112 138
 Bumpus H C (1921) *Surg Gyn Obst* 32 31
 Cappell D F (1935) *Glasgow Med J* 124 177
 Cooray G H (1944) *Indian J Med Res* 32 71
 Engle E T and Stout A P (1940) *Amer J Cancer* 39 334
 Feldman W H (1932) *Neoplasms of Domesticated Animals* Philadelphia
 Fergusson J D and Pagel W (1945) *Brit J Surg* 33 122
 Fischer Defoy W (1905) *Z Krebsforsch* 3 195
 Fronz W A and Alyea E P (1928) *J Urol* 20 135
 Gaynor E P (1938) *Virchows Arch* 301 602
 Gordon H (1941) *Urol Cutan Rev* 45 646
 Guibal P, and Pavie P (1929) *Ann Anat path* 6 1099
 Gutman A B Gutman E B and Robinson J N (1940) *Amer J Cancer* 38 103
 Haddow A (1943) *Brit J Urol* 16 193
 Horning E S (1946) *Lancet* ii 829
 Huggins C and Hodges C V (1941) *Cancer Res* 1 293
 Joll C A (1923) *Brit J Surg* 11 38
 Junghanns H (1930) *Dtsch Z Chir* 224 418
 Kahler J E (1939) *J Urol* 41 557
 KAUFMANN E (1902) *Pathologische Anatomie der malignen Neoplasmen der Prostata*
Dtsch Chir 53 381 (An excellent account)
 Klissurow A (1928) *Virchows Arch* 268 515
 Lundsgaard C (1913) *Virchows Arch* 213 55
 Moore R A (1935) *J Urol* 33 224
 MOORE, R A (1944) Benign hypertrophy and carcinoma of the prostate *Surgery* 16 152
 (A useful review with many references)
 Moore R A and Melchionna R H (1937) *Amer J Cancer*, 30 731
 Muir E G (1934) *Lancet* i 667
 Nicholson G W (1923 and 1924) *Guy's Hosp Rep* 1923 73 298 1924 74 81

lymph nodal metastases may sometimes invade neighbouring vertebral veins whence the tumour may spread into the adjacent bones, or that following establishment of secondary growths in the vertebrae by this or the more usual embolic route, invaded vertebral veins may be a route of local direct or embolic spread within the bones or from one bone to another. The involvement of several neighbouring vertebrae in a large mass of secondary growth as in Case I Fig 292 ✓

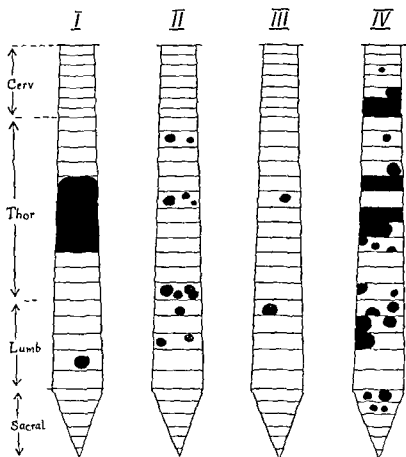


FIG. 292 —Diagram to show distribution of spinal metastases in 4 cases of prostatic carcinoma

Case I aged 83 all other bones clear including pelvis small metastases present in lungs

Case II aged 66 metastases also in sternum and skull but not in pelvis no visible metastases in lungs

Case III aged 70 metastases also in pelvis and sternum small metastases present in lungs

Case IV aged 64 metastases also in pelvis and sternum small metastases present in lungs

may well be due to such local spread from a single initial metastasis in one of the bones. It may be mentioned too that Roberts studying the spinal metastases of prostatic cancer found extensive plaques of growth on the deep surfaces of the laminae and ligaments and suggested that the lymphatics of the ligaments and neighbouring tissue might be an important route of extension of the growths within the spine from bone to bone. ✓

Warren and co workers while agreeing that the metastasis of prostatic cancer to bones often takes place by the blood stream advanced reasons for believing that perineural lymphatics afford an important auxiliary route of metastasis to

CHAPTER 35

EPIDERMOID CARCINOMA OF THE PENIS AND SCROTUM

IN STRUCTURE and behaviour tumours of the epidermis of the scrotum and penis resemble those of the skin generally (q v). Basal cell growths and tumours of the cutaneous glands are, however, very rare in these sites. Because of differences in causation epidermoid growths of the penis and scrotum must be considered separately from those of the rest of the skin and from each other. As in other situations no sharp distinction can be made between papilloma and carcinoma, the one is only the non invasive form, and the other the invasive form of the same kind of growth, and all transitions are seen.

EPIDERMOID CARCINOMA OF THE PENIS

(I) Incidence and causation

(a) *Frequency and race*

Almost all penile neoplasms are epidermoid carcinomas, carcinomas of the penile urethra are rare, and non epithelial tumours of the penis are rarer still. Some of the few supposed instances (e.g. the 'endothelioma' reported by Colmers) clearly being carcinomatous. In most European countries and in America penile cancer is a relatively infrequent tumour, e.g. in England and Wales during 1930-1932 there were 496 deaths from penile cancer as compared for example with 18,876 deaths from gastric cancer, 3,225 from lingual cancer and 2,668 from vesical cancer in males (Registrar General's Decennial Supplement, 1938).

Although accurate comparisons are not possible it is clear that penile cancer is much commoner amongst the Oriental races, especially the Indians and Chinese, than amongst Europeans. Thus in Nath and Grewal's analysis penile cancer ranked high in the lists of tumours studied in Indian hospitals, accounting for about one tenth of all cases of malignant disease in males in most communities, and it accounted for 248 of 1,815 carcinoma biopsies reported by Cooray from Ceylon and for 18 per cent of cancers in Chinese (Ngai).

(b) *Circumcision*

Circumcision is undoubtedly the main factor responsible for the racial differences of incidence of penile cancer, and no genetic differences in susceptibility need be postulated. Amongst the Jews of all countries, who regularly circumcise in infancy, penile cancer is very rare, perhaps indeed non-existent (Sorsby). Amongst Mohammedans, who defer circumcision until childhood or adolescence, the disease occurs occasionally. The sharp contrast between the rarity of penile cancer in Mohammedans and its great frequency in the uncircumcised Hindus in the same communities is well shown in Nath and Grewal's figures. Ngai found phimosis in 87 of 88 Chinese patients. Clinicians and pathologists have of course long recognized that penile cancer in Europeans is

- PÜRCKHAUER, R (1929) Das Prostatacarcinom seine Häufigkeit und seine Metastasen
Z Krebsforsch 28 68
- von Recklinghausen F (1891) *Festschrift Virchow's 71. Geburtstag* p 17
- Rich A R (1935) *J Urol* 33 215
- Roberts O W (1927) *Brit J Surg* 15 652
- Rudduck H B and Willis R A (1938) *Amer J Cancer* 33 205
- Schenken J R, Burns E L and Kahle P J (1942) *J Urol* 48 99
- Schlotthauer C F and Millar J A S (1941) *J Amer Vet Med Assoc* 99 239
- Trachsler W (1934) *Z Krebsforsch* 41 382
- Warren S, Harris P N and Graves R C (1936) *Arch Path* 22 139
- Watkinson J M, Delory G E, King E J and Haddow A (1944) *Brit Med J* ii 492
- Willis R A (1934) *The Spread of Tumours in the Human Body* p 196 London
- ZEMGULAS J (1931) Krebsmetastasen im Knochensystem mit besonderer Berücksichtigung der Wirbelsäule und der Osteophytosis carcinomatosa, *Z Krebsforsch* 34 266

glans or prepuce and without signs of infiltration of the deeper tissue. They may long remain in this stage, slowly extending, but eventually invasive carcinoma supervenes.

(3) Spread and metastasis

Besides extending to and perforating the overlying prepuce, the tumours often invade the urethra and *corpora cavernosa* and *spongiosa*. Some tumours spread preferentially within the vascular spaces of the erectile tissue (Kuttner, Colmer) and it is possible that local embolic metastases may also occur in this tissue for areas of growth apparently separate from the main mass are sometimes to be found in more proximal parts of the erectile bodies.

Metastases in lymph glands develop at some stage of the disease in a high proportion of cases, 60 per cent according to Barney. Although enlargement of the inguinal glands is usually present at an early stage, this is often due to inflammation only, tumour metastasis usually occurring relatively late (Kuttner, Lane Claypon). Microscopical examination of the glands is therefore important for prognosis. Kuttner found that in occasional cases the pelvic lymph glands were affected earlier than the inguinal glands.

Blood borne metastases have only occasionally been reported (Barney, Kuttner, Ngai).

EPIDERMOID CARCINOMA OF THE SCROTUM

(1) Incidence and causation

(a) Frequency and race

In England and Wales deaths from scrotal cancer are about half as numerous as those from penile cancer, e.g. 209 and 496 cases respectively during the years 1930-1932. In native races and non industrialized countries, cancer of the scrotum occurs but rarely, if ever, the Kennaways could find no instances of this disease even from countries where penile cancer is common.

(b) Occupational and social factors

Chimney sweeps' cancer was the first tumour to be clearly recognized as occupational, by Pott in 1775. The most recent and detailed accounts of occupational cancer of the scrotum are those of Hueper (1942) and of Henry (1946) while the Kennaways' papers also give valuable analyses. In the majority of cases scrotal cancer is clearly attributable to occupational factors occurring in chimney sweeps, cotton mule spinners and gas, tar pitch and creosote workers and there is little doubt that benzpyrene and other carcinogenic hydrocarbons are the offending agents. Further, victims of this disease in occupations not recognized as hazardous almost all belong to the industrial or other manual labouring classes professional and clerical workers being almost exempt from scrotal cancer. This therefore appears to be a form of cancer that is wholly, or almost wholly dependent on environmental factors" (Kennaway and Kennaway). The Kennaways suggest that those persons who from choice

much more frequent in the uncircumcised than in the circumcised and that phimosis is present in a high proportion of patients with this disease more than one half of them according to Lane Claypon. It is probable that penile cancer could be eliminated by general adoption of circumcision in infancy. It is for future research to show whether or not carcinogenic substances are generated in retained smegma.

(c) *Other possible carcinogenic factors*

As the Kennaways have shown carcinoma of the penis contrasts sharply with carcinoma of the scrotum in that its incidence shows no distinct relationship to occupation or social class. This supports the view that the main factor in causation is the presence of the prepuce, and that extrinsic carcinogens play little or no part. Although examples are recorded of carcinomas arising in or near the scars of former chancres (Barney, Leighton) it is doubtful whether venereal or other infections predispose significantly to the disease.

(d) *The distribution of the tumours*

This also supports the view that extrinsic factors are of little importance in causation. The almost invariable sites of origin are the glans or inner surface of the prepuce. carcinoma of the skin of the penis or of the outer surface of the prepuce is rare.

(e) *Age*

The mean age of European patients at the time of treatment is between 52 and 54 (Lane Claypon) and the disease has only occasionally been observed in men under 30 (references by Leighton). In Orientals however the average age of patients is about a decade less than in Europeans e.g. 44 in Ngai's series.

(f) *Penile carcinoma in animals*

This is one of the commonest tumours in the horse and it occurs also in the ox, dog and cat (Feldman). Rudduck and I saw also two examples of carcinoma of the skin of the abdominal wall close to the prepuce in dogs.

(2) *Structure and growth*

The tumours are papillary or infiltrating epidermoid growths similar to those of the rest of the skin. In their early stages they may long remain superficial and papillomatous and this papillomatous change may take place over a wide area of the surface of the glans and prepuce or multiple areas of growth may be found. Papillary tumours may form large exuberant masses before showing much invasiveness but this does not justify their separation as a distinct group from the more invasive ulcerative form of growth. It is not unusual for a well advanced growth to remain long hidden and unsuspected in a patient with phimosis.

A rare form of tumour is intra-epidermal carcinoma *in situ* this is the counterpart of Bowen's disease of the skin and has been called 'Paget's disease' of the penis and erythroplasia, names which as urged in Chapter 14 denote only variants of the one kind of lesion. Intra-epidermal carcinoma of the penis appears as single or multiple shiny red or encrusted patches, flush with the surface of the

glans or prepuce and without signs of infiltration of the deeper tissue. They may long remain in this stage, slowly extending but eventually invasive carcinoma supervenes.

(3) Spread and metastasis

Besides extending to and perforating the overlying prepuce, the tumours often invade the urethra and *corpora cavernosa* and *spongiosa*. Some tumours spread preferentially within the vascular spaces of the erectile tissue (Kuttner, Colmers), and it is possible that local embolic metastases may also occur in this tissue, for areas of growth apparently separate from the main mass are sometime to be found in more proximal parts of the erectile bodies.

Metastases in lymph glands develop at some stage of the disease in a high proportion of cases, 60 per cent according to Barney. Although enlargement of the inguinal glands is usually present at an early stage, this is often due to inflammation only, tumour metastasis usually occurring relatively late (Kuttner, Lane Claypon). Microscopical examination of the glands is therefore important for prognosis. Kuttner found that in occasional cases the pelvic lymph glands were affected earlier than the inguinal glands.

Blood borne metastases have only occasionally been reported (Barney, Kuttner, Ngai).

EPIDERMOID CARCINOMA OF THE SCROTUM

(1) Incidence and causation

(a) Frequency and race

In England and Wales deaths from scrotal cancer are about half as numerous as those from penile cancer, e.g. 209 and 496 cases respectively during the years 1930-1932. In native races and non industrialized countries, cancer of the scrotum occurs but rarely, if ever, the Kennaways could find no instances of this disease even from countries where penile cancer is common.

(b) Occupational and social factors

Chumney sweeps' cancer was the first tumour to be clearly recognized as occupational, by Pott in 1775. The most recent and detailed accounts of occupational cancer of the scrotum are those of Hueper (1942) and of Henry (1946), while the Kennaways' papers also give valuable analyses. In the majority of cases scrotal cancer is clearly attributable to occupational factors occurring in chumney sweeps, cotton mule spinners, and gas, tar, pitch and creosote workers, and there is little doubt that benzpyrene and other carcinogenic hydrocarbons are the offending agents. Further, victims of this disease in occupations not recognized as hazardous almost all belong to the industrial or other manual labouring classes, professional and clerical workers being almost exempt from scrotal cancer. This therefore "appears to be a form of cancer that is wholly, or almost wholly dependent on environmental factors" (Kennaway and Kennaway). The Kennaways suggest that those persons who from choice

or professional necessity wash most are the least liable to scrotal cancer and that in cases of this disease in which no definite occupational hazard has existed the disease may be due to lack of cleanliness in those exposed to coal smoke, in other words, possibly all town dwellers are in some slight degree liable to chimney sweeps cancer

(c) *Site*

Most of the tumours are situated on the anterior and lateral aspects of the scrotum, and rather more often on the left side than on the right (Henry)

(d) *Age*

When in Pott's day boys were engaged as chimney sweeps it was not unusual for scrotal cancer to occur in children or adolescents (references by Hueper). With increasing recognition of this and allied occupational risks and the introduction of protective legislation however youthful cases ceased to occur and the mean age of the victims of scrotal cancer steadily increased until it now lies late in the sixth or in the seventh decade (Henry). Henry also draws attention to the long periods of exposure necessary for the induction of the disease—from 16 to 50 years after commencing work in the hazardous occupation. The disease may develop many years—up to 35 years—after retirement from work. Henry mentions one man who started work in the mule room at the age of 6 and developed scrotal carcinoma at 75–10 years after retirement.

(2) *Structure, growth and metastasis*

What has already been said of epidermoid carcinoma of the penis and of the skin generally applies to that of the scrotum. Benign warts may long precede invasive malignancy. Multiple growths are fairly common. The tumours are of the usual cornifying type, seldom growing very rapidly but eventually extending widely to surrounding parts and ulcerating, producing inflammatory enlargement of the inguinal lymph glands at early stages and metastases in the glands at later stages and occasionally disseminating by the blood stream.

REFERENCES

- Barney J D (1907) *Ann Surg* 46 890
 Colmers F (1903) *Beitr path Anat* 34 295
 Cooray G H (1944) *Indian J Med Res* 32 71
 Feldman W H (1932) *Neoplasms of Domesticated Animals* Philadelphia
 HENRY, S A (1946) *Cancer of the Scrotum in Relation to Occupation* London (A valuable well illustrated monograph)
 Hueper W C (1942) *Occupational Tumors* Springfield
 KENNAWAY, F I and KENNAWAY, N M (1946) The social distribution of cancer of the scrotum and cancer of the penis *Cancer Res* 6 49 (Contains references to the authors' important earlier papers)
 Kuttner H (1900) *Beitr klin Chir* 26 41
 Lane Claypon J E (1930) *Rep Pub Health Med Subj* No 59
 Leighton W E (1932) *Amer J Cancer* 16 251
 Morson A C (1930) *Proc Roy Soc Med* 23 667
 Nath V and Grewal K S (1935) *Indian J Med Res* 23 149
 Nath V and Grewal K S (1937) *Ibid* 24 633

Nath V and Grewal, K S (1939) *Ibid*, 26 785

NGAI, S K (1933) "The etiological and pathological aspects of squamous-cell carcinoma of the penis among the Chinese", *Amer J Cancer*, 19 259 (A valuable well illustrated account)

Sorsby M (1931) *Cancer and Race* London

or professional necessity wash most are the least liable to scrotal cancer, and that in cases of this disease in which no definite occupational hazard has existed the disease may be due to lack of cleanliness in those exposed to coal smoke, in other words, possibly all town dwellers are in some slight degree liable to chimney sweeps' cancer'

(c) Site

Most of the tumours are situated on the anterior and lateral aspects of the scrotum and rather more often on the left side than on the right (Henry)

(d) Age

When in Pott's day, boys were engaged as chimney sweeps it was not unusual for scrotal cancer to occur in children or adolescents (references by Hueper). With increasing recognition of this and allied occupational risks and the introduction of protective legislation, however, youthful cases ceased to occur and the mean age of the victims of scrotal cancer steadily increased until it now lies late in the sixth or in the seventh decade (Henry). Henry also draws attention to the long periods of exposure necessary for the induction of the disease—from 16 to 50 years after commencing work in the hazardous occupation. The disease may develop many years—up to 35 years—after retirement from work. Henry mentions one man who started work in the mule room at the age of 6 and developed scrotal carcinoma at 75—10 years after retirement.

(2) Structure, growth and metastasis

What has already been said of epidermoid carcinoma of the penis and of the skin generally applies to that of the scrotum. Benign 'warts' may long precede invasive malignancy. Multiple growths are fairly common. The tumours are of the usual cornifying type, seldom growing very rapidly, but eventually extending widely to surrounding parts and ulcerating, producing inflammatory enlargement of the inguinal lymph glands at early stages and metastases in the glands at later stages and occasionally disseminating by the blood stream.

REFERENCES

- Barney J D (1907) *Ann Surg* 46 890
 Colmers F (1903) *Beitr path Anat* 34 295
 Cooray G H (1944) *Indian J Med Res* 32 71
 Feldman W H (1932) *Neoplasms of Domesticated Animals* Philadelphia
 HENRY S A (1946) *Cancer of the Scrotum in Relation to Occupation* London (A valuable well illustrated monograph)
 Hueper W C (1942) *Occupational Tumors* Springfield
 KENNAWAY E L and KENNAWAY, N M (1946) The social distribution of cancer of the scrotum and cancer of the penis *Cancer Res* 6 49 (Contains references to the authors' important earlier papers)
 Kuttner H (1900) *Beitr klin Chir* 26 41
 Lane Claypon J E (1930) *Rep Pub Health Med Subj* No 59
 Leighton W E (1932) *Amer J Cancer* 16 251
 Morson A C (1930) *Proc Roy Soc Med* 23 667
 Nath V and Grewal K S (1935) *Indian J Med Res* 23 149
 Nath V and Grewal K S (1937) *Ibid* 24 633

is certainly false (The rather distinctive 'Hurthle cell' adenoma is considered along with carcinoma)

(2) Behaviour

Most thyroid adenomas grow only slowly, and cessation of growth with degenerative changes is frequent. Yet a long standing apparently stationary tumour may become a "malignant adenoma" and produce metastases. In addition to histological anaplasia and mitotic activity of suspicious degree in a tumour regarded as an 'adenoma', there are two other structural features which for prognostic purposes place tumours of otherwise 'benign' appearance in the 'malignant adenoma' class. These are (a) predominant papillary structure, and (b) invasion of blood vessels.



FIG. 293—Colloid adenoma with much oedematous stroma ($\times 90$)

(a) Papillary adenomas cannot be distinguished from papillary carcinomas, Dunhill in his large experience saw only two tumours which he regarded as "benign papillomas", and one of these later recurred. I have seen two instances of infiltrative recurrence of tumours initially diagnosed as papillary adenomas. Here is the history of one of these.

Case I—In April 1932 a woman of 44 years had had a slowly enlarging rounded tumour in her neck for 7 years. At operation a well-circumscribed cystic adenoma 10 centimetres in diameter was evacuated and enucleated. Microscopical diagnosis was highly papillary adenoma potentially malignant. Slow recurrence took place and in June 1935 a firm ill-defined mass of growth was excised. This again showed well organized papillary growth identical with that removed 3 years earlier. Further recurrence later took place and was deemed inoperable because of adhesion to the trachea.

CHAPTER 36

EPITHELIAL TUMOURS OF THE THYROID GLAND

IN THE thyroid gland as in many other organs, no sharp separation of epithelial hyperplasias, benign tumours and malignant tumours is possible. Nodular areas of hyperplasia in goitrous organs become adenomatous. Structural distinction between adenoma and carcinoma is often impossible, and not a few benign adenomas of long duration eventually prove malignant by invading blood vessels and metastasizing, sometimes with little or no change of structure. Of course it is convenient and necessary to assign thyroid overgrowths to one or another group and in most cases the behaviour of the lesions corresponds with the experienced pathologist's opinion. An *adenoma* is a well circumscribed encapsulated tumour with no evidence of invasive growth or metastasis. A *carcinoma* is a tumour of any structure which shows evidence of invasive growth or metastasis; its histological structure usually betrays its malignancy but is sometimes benign in appearance, resembling in part that of any of the forms of adenoma or even of normal thyroid tissue. The rare *mixed tumours* containing both epithelial and mesenchymal components will require separate consideration.

ADENOMAS

I do not propose to repeat in detail the well known features of these common tumours (*see* Marine, Tebbutt and Woodhill and Joll). Most of them arise in goitrous thyroids; they are therefore more frequent in endemic goitrous regions than in others, they affect women more than men and may be single or multiple. They vary greatly in naked eye appearance, the tissue of some having the typical vesicular structure of normal thyroid or colloid goitre and that of others being solid and opaque, cystic change, haemorrhage, pigmentation, fibrosis and calcification are frequent.

(1) Microscopic structure

This, like the naked eye appearance, varies greatly. Colloid filled vesicles of all sizes and shapes, well differentiated acini devoid of colloid, poorly differentiated acini or almost diffuse sheets of epithelial cells, and papillary structures with or without colloid, are found (Figs 293-294). The stroma is often oedematous, poorly fibrous and plentiful, sometimes so abundant as to give the tumours a semi-fluid translucent appearance. Some tumours show predominance of one or other type of structure; others show several or all of the possible structural variants. Mitosis is scanty in benign adenomas, whether of well differentiated vesicular or poorly differentiated types. Squamous metaplasia, as in the specimen depicted by Nicholson in his Fig 71, is rare. Attempts to subdivide adenomas into colloid, foetal and mixed varieties are futile and unnecessary and persistence of the term *foetal* is unfortunate for Wolfer's view that adenomas of predominantly non-colloid structure arose from rests of immature tissue.

(b) Age incidence

This differs little from that of carcinoma in general. The peak of the age distribution curve of Pack and Le Fevre's clinical series lay in the second half of the sixth decade, and the mean age was 53 years. The mean age of males in Pemberton's series was 53, of females 48, and 70 per cent of all cases were between the ages of 40 and 70 years. The mean age at death of my 9 necropsy cases was 70 years. The disease rarely appears in people less than 35 years old, but it may occur even in childhood, e.g. Pemberton's series included 4 patients under 10, all girls, the youngest aged 7.

(c) Sex

In most series of cases there is a decided excess of females over males, e.g. 3 to 1 in the mortality figures of England and Wales 1918-30 (Joll), 3 to 1 in Pack and Le Fevre's clinical series, and 1.7 to 1 in Pemberton's series. Cooray's Cingalese patients were 24 women and 14 men, and all 7 of Quinland and Cuff's Negro patients were women.

(d) Previous goitre

This is recorded in a high proportion of cases—between 25 and 60 per cent of cases in populations in which goitre is not specially prevalent, and in even higher proportions of cases in goitrous regions. It is clear that nodular goitre and adenoma predispose to carcinoma (see Wegelin's figures cited above). In a high proportion of cases, probably the majority, carcinomas arise in pre-existing adenomas. Graham and others placed this proportion as high as 90 per cent, but, as Pemberton has pointed out, some long-standing supposedly benign adenomas may possess low-grade malignancy *ab initio*. Cole *et al.*, in a good discussion of nodular goitre as a pre-cancerous lesion, found that 37 per cent of their carcinomas definitely arose in adenomas, but considered that the actual proportion was certainly greater than this, the carcinoma doubtless having submerged the original adenoma in many cases.

(2) Adenomas and carcinomas of the thyroid in animals

Thyroid adenomas and carcinomas—it is often uncertain which—have been reported in many species of animals, including fish as well as dogs, horses, cattle, sheep, guinea pigs and rats (Ewald, Wegelin, Feldman, Hellwig, Davis). As in man, so in animals, goitre usually precedes the development of tumours. Metastasizing carcinomas of the thyroid are common in dogs, especially in endemic goitrous areas, large veins are often invaded by tumours and metastases occur principally in the lungs (Davis).

(3) Structure

Individual tumours may show predominance of one or another of the following types of structure, or several or all of these variants may be found in one tumour.

(a) *Colloid containing vesicular adenocarcinoma*, resembling normal thyroid

The discovery that an enucleated tumour has a papillary structure however highly organized and quiescent in appearance, calls for at least partial thyroidectomy of the tumour bearing part of the organ and a guarded prognosis

(b) Demonstrable invasion of small veins in an 'adenoma' or its capsule places it unequivocally in the malignant class. As Ehrhardt Erdheim Graham Warren and Dunhill have all shown later recurrence or metastasis from such tumours is frequent however "benign" their structure

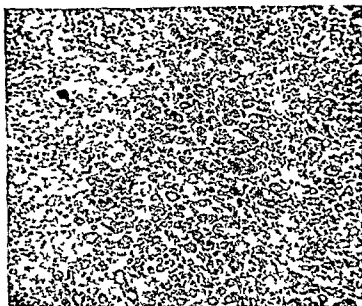


FIG 294—So-called foetal adenoma with small vesicles without colloid and undifferentiated diffusely scattered epithelium ($\times 75$)

CARCINOMAS

(1) Frequency and causation

(a) Frequency

The frequency of cancer differs greatly in different communities, according to the prevalence of goitre. Thus Beirard and Dunet (cited by Wegelin) concluded that in endemic goitrous regions from 2.5 to 4 per cent of all malignant tumours arose in the thyroid but in goitre free areas less than 0.5 per cent. Wegelin noted the much greater incidence of thyroid cancer in necropsies in Berne the centre of a goitrous area than in Vienna Prague Berlin or the United States of America. The ratio of malignant to non malignant enlargements of the thyroid seen in hospital practice in Great Britain is indicated by Vaux's figures: he found 25 cases of malignant disease in 722 cases of goitre (3.5 per cent) and cited other series showing proportions ranging from 1 to 5 per cent. Various native races get thyroid cancer e.g. the Cingalese (Cooray), Tanganyikans (Connell), Bantus (Strachan), Negroes (Quinlind and Cuff).

vesicular characters is a frequent form of growth, inseparable from papillary adenoma (Figs 296 and 300) This is the kind of growth which is prone to metastasize locally to the cervical lymph glands and to grow slowly there, simulating a 'lateral aberrant thyroid' (see below)

- (d) *Carcinoma simplex* occurs alone or along with other structural variants. It may be of alveolar polyhedral celled type, or may be diffuse and pleomorphic celled and readily mistaken for sarcoma (Fig 297). Multinucleated giant tumour cells are common in anaplastic carcinoma. There is no doubt that most of the reported 'sarcomas' and "carcino sarcomas" of the thyroid have been anaplastic carcinomas.
- (e) *Squamous cell structure* resulting from metaplasia is rare (Nicholson, Pemberton).
- (f) So called "Hurthle cell" structure (see below)



Fig 297—Diffuse pleomorphic-celled part of the primary growth from the same case as Fig 296 ($\times 120$)

Thyroid carcinoma is remarkable for the diversity of structure which may be found in one tumour, as in the tumour described by Rosenthal and Willis in the tumour depicted in Figs 296 and 297, and in Case IV below. On the other hand, some of the cystic papillary growths show remarkable uniformity of structure during a long metastatic career, and some of the highly anaplastic growths consist of similar diffusely cellular tissue throughout. (For good accounts and illustrations of the range of structure in thyroid carcinomas see Bell, Graham, Smith *et al*, Dunhill, Haagenesen, Vaux and Joll.)

(4) "Hurthle-cell" tumours

The so called "Hurthle cell" tumours require separate mention, because of their rather distinctive structure and because of the doubtful propriety of the name

or colloid goitre (Fig 295) is the structure which, when found preponderating in secondary growths in bones, led Cohnheim and others to speak of 'benign metastasizing goitre'

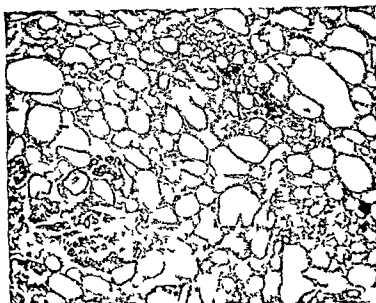


FIG 295 —Well differentiated colloid vesicular structure in a pulmonary metastasis of thyroid carcinoma from a man aged 69 ($\times 60$)



FIG 296 —From a lymph nodal metastasis of cystic papillary adenocarcinoma in a woman aged 81 ($\times 120$)

- (b) *Non colloid acinar adenocarcinoma* of variable degrees of differentiation often accompanies (a)
- (c) *Papillary adenocarcinoma* often cystic and often associated with colloid



FIG 299—Case II Carcinoma of lingual thyroid A = large-eosinophil-celled tubular structure B = clear-celled structure C = invasion of lingual muscle ($\times 100$)

but there are also malignant members of the group which recur or metastasize (Haagensen Martin and Eikin) Most of the tumours have appeared in adults but Symmers saw a congenital one The tumour of the lingual thyroid in Case II below was partly of large eosinophilic celled type

Many writers from Langhans onwards, described large celled alveolar tumours of the thyroid, and several different hypotheses were advanced ascribing a special histogenesis to them some even supposing them to be of parathyroid origin. A resemblance between the large eosinophilic cells of the tumours and the interfollicular cells described by the histologist Hurthle in 1894, led some pathologists to adopt the eponymic name now in current use. This is treble unfortunate—first, because there is no real evidence that the tumours are related to the cells described by Hurthle; secondly, because the very existence of special interfollicular cells in the thyroid is doubtful (Joll) and thirdly because, even if special cells of this kind exist and the tumours arise from them the eponymic name is inappropriate since Baber described the same cells 17 years before Hurthle (see Nonidez, and Wilensky and Kaufman).



FIG. 298.—Large-eosinophil-celled (Hurthle-cell) tumour ($\times 120$)

These large eosinophilic celled adenomas and adenocarcinomas of the thyroid almost certainly arise not from any special source but from the ordinary thyroid epithelium and constitute only one of the many structural variants of which its tumours are capable. Tumours with this structure predominant appear to the naked eye as well circumscribed solid homogeneous opaque white or yellow growths and consist microscopically mainly of large eosinophilic finely granular or foamy polygonal cells arranged in solid trabeculae or around small acinar spaces (Fig. 298). Some tumours show extensive areas of clear celled structure like that of renal adenocarcinomas which indeed can be closely simulated, and as Wilensky and Kaufman noted parts of the tumours may show the more usual structural variants of thyroid carcinomas. Many of the tumours are benign in that they grow slowly are well circumscribed and do not recur after removal.

(a) *Metastases in lymph glands*

Regional lymph nodal metastases are common from infiltrative growths, whether of papillary or anaplastic types, but they are often long delayed or absent in cases of "malignant adenoma" in which the tumour is still largely confined within the adenoma capsule. The following case exemplifies metastasis to the regional glands from papillary adenocarcinoma.



FIG 300—Case III. Cystic papillary adenocarcinoma metastatic in a lymph gland. Arrows point to calcified spherules; colloid vesicles are marked X. ($\times 100$)

Case III (Mr Balcombe Quick's case)—In November 1936 a man aged 34 first noticed multiple lumps in the left side of his neck, and 2 months later in his axilla. In October 1937 enlarged axillary lymph glands were excised and found to contain cysts filled with colloid and lined by simple cuboidal epithelium. Further enlarged glands slowly developed, and in February 1939 several cervical glands containing cysts filled with brownish fluid were removed and found microscopically to show papillary adenocarcinoma of thyroid origin metastatic in lymph glands (Fig 300). In view of this report left hemithyroidectomy was performed although the gland was not palpably enlarged; more glands in the anterior triangle were also removed. The thyroid was found to contain an ill-defined area of scirrhous adenocarcinoma 1.5 centimetres in diameter which was quite impalpable and invisible from the surface of the gland. The lymph glands contained multiple small deposits of papillary growth similar to that removed earlier. In March and April the posterior triangle and axilla were explored and cleared of glands some of which contained deposits of similar growth. Deep X ray therapy was begun in May and the patient remained well at the end of 1939.

'*Lateral aberrant thyroids*'—Do they exist or are they always metastases in the cervical lymph glands from small unsuspected primary carcinomas of the thyroid? This question raised by cases like the foregoing has been discussed by Tebbutt and Woodhull, Dunhill, Crile, Frantz *et al* and King and Pemberton. In many of the supposed cases of "lateral aberrant thyroids", the authors have

(5) Carcinoma of the lingual thyroid

Wapshaw has reviewed the few recorded cases of carcinoma of the lingual thyroid and the following case exemplifies this rare condition

Case II (Mr A F MacLure's case)—A man of 26 complained of difficulty in swallowing for several months. Examination showed a rounded slightly lobulated sub epithelial mass 5 centimetres in diameter in the base of the tongue. This was excised with some difficulty because it infiltrated the muscle at its margins. It consisted of solid white tissue. Microscopically (Fig 299) it presented solid masses and trabeculae or irregularly hollow tubules of large epithelial cells most of which showed solid eosinophilic cytoplasm while others were vacuolated and empty in appearance. No colloid-containing vesicles could be found. The tumour subsequently recurred and proved fatal but details are not known.

(6) Function in thyroid carcinoma

Since other ductless glands are the sites of hypersecreting tumours and since parts of many thyroid carcinomas show a high degree of structural differentiation, we might expect signs of hyperthyroidism to accompany many of these tumours. The proportion of cases in which this occurs however is relatively small and the interpretation often far from clear.

In the much quoted classical case of Eiselsberg (1894) total excision of the adenomatous thyroid was followed by signs of sub thyroidism. Subsequently metastatic adenocarcinoma developed in the sternum and the sub thyroid symptoms improved, excision of the sternal tumour was followed by return of symptoms, later still a tumour developed in the scapula but without further improvement. Mori collected the older literature of associated thyroidoma and signs of thyrotoxicosis. Pemberton found that in one third of with malignant thyroid tumours, the basal metabolic rates were above

In Friedell's series hyperthyroidism was diagnosed in 57 of 412 adenocarcinoma (13.8 per cent) this was more frequent with well differentiated than with poorly differentiated growths and with non papillary than papillary ones. From Friedell's findings it appears probable that hyperthyroidism by well differentiated adenocarcinomas indeed contributes to the hyperthyroid symptoms. But the question is complicated by the frequent presence of hyperthyroidism in other parts of the cancerous thyroids. These parts may be mainly to blame for the thyrotoxic symptoms which may be aggravated as the result of invasive effects and pressure or vascular disturbances occasioned by the carcinoma. There is no evidence that the thyrotoxic thyroid is particularly predisposed to tumour formation. Reports of patients with exophthalmic goitre later developing carcinoma are rare.

(7) Growth and metastasis

No other kind of carcinoma shows a wider range of rate of growth and metastatic behaviour than thyroid carcinoma. At the one extreme, there are the very indolent highly differentiated cystic papillary growths which metastasize to the neighbouring cervical lymph glands and spread slowly from gland to gland over a long period of years. At the other extreme there are the highly anaplastic sarcoma like growths which grow quickly to a huge bulk or disseminate rapidly and widely by the blood stream.

the blood stream, multiple metastases in lungs or bones commonly appear before the cervical lymph glands are affected, and often these metastases are the first signs of disease

Metastases in bones occur in at least one third of all fatal cases of thyroid carcinoma. They are most frequent from "malignant adenomas", and the structure of parts of the skeletal growths is often highly differentiated and thyroid like. Of course, Cohnheim's concept of "benign metastasizing goitre" has now only historical interest, as Berard and Dunet, Joll, Bell, Simpson and others showed, adequate examination of metastasizing thyroid tumours will always reveal ample structural evidence of carcinoma. The skeletal metastases of thyroid

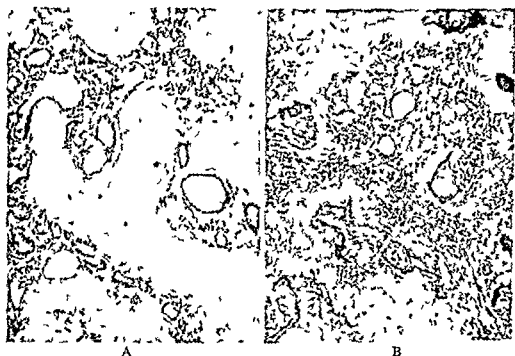


FIG 301 —Mixed tumour from a dog showing closely mingled glandular tissue and ossifying and cartilaginous tissue. A is from primary tumour in thyroid. B from an extension within a large thyroid vein. ($\times 70$)

carcinomas sometimes pulsate, as in the case which Rosenthal and I described, and pulsating metastases have been mistaken for aneurysms (Halbrecht, Rhea). For other details regarding metastases in bones and diagnostic errors caused by them, see Eiselsberg, Gierke, Joll (1923) and my 1934 work.

MIXED TUMOURS OF THE THYROID

Not uncommonly in dogs, but rarely in man, there occur mixed tumours of the thyroid containing both thyroid epithelial tissue and neoplastic mesenchymal tissue, usually osteogenic or cartilaginous. Funkenstein (1903) reviewed the few previous reports (Zahn's and Pick's) of such tumours in both dogs and man, and described two malignant "osteochondrosarcomas" arising in human goitrous thyroids. He supposed the thyroid tissue which was present in these to be only included residues of goitrous tissue, for in his first case, as also in

remarked on their proneness to low grade papillary growth, their multiplicity their association with lymph glandular tissue and the frequent enlargement of the corresponding lobe of the thyroid Crile, reporting 13 cases of 'papillary tumors of lateral aberrant thyroids', noted of nearly one half of the cases that the corresponding lobe of the thyroid contained similar growth, yet he concluded that the tumours are 'essentially benign' and that it is probable that many cases reported as papillary carcinoma of the thyroid with metastasis to the regional lymphatics are in reality benign papillary lateral aberrant thyroids with a coexistent benign tumor in the thyroid gland Crile's conclusion that lateral thyroids are essentially benign is markedly at variance with the findings of all other writers on this subject For example Frantz *et al* in 30 cases of lateral thyroid concluded that these showed malignant properties in 23 patients, 8 of whom had died of the disease

From Case III above and several similar cases I have seen and from my study of the literature, I think that the evidence fully warrants King and Pemberton's conclusion that 'so called lateral aberrant thyroid tumors are nearly always metastatic extensions to the deep cervical lymph nodes from a primary carcinoma in the homolateral lobe of the thyroid gland' I had come to the same conclusion before I read King and Pemberton's excellent paper, and I would go even further and say that there is no evidence that developmentally aberrant thyroid tissue ever occurs in the lateral position Sir Arthur Keith who has had a wide experience of developmental anomalies of the head and neck, informs me that he has never seen or read of an unequivocal instance of the presence of a mass of detached normal thyroid in the lateral position A 'lateral aberrant thyroid' calls for hemithyroidectomy and if this is done a small carcinoma will always be found, if searched for in the excised lobe

The following case also recorded elsewhere (Willis 1941 Case 441) exemplifies not only diagnostic difficulty caused by metastases in lymph glands but also the wide variety of structure which a thyroid carcinoma may show

Case IV—History—A woman of 62 was admitted to hospital with a mass 10 centimetres in diameter noticed enlarging for 3 weeks in her right axilla This was incised as an abscess no pus was found and a piece of tissue which was removed showed a rapidly growing round-celled tumour thought to be a sarcoma *Necropsy* 4 weeks later showed that although the thyroid was not enlarged its right lobe was replaced by soft white growth microscopically showing diffuse round-celled growth like that from the axilla but with acinar formation in places Multiple metastases were present in the cervical and axillary lymph glands and in the lungs and kidney The vertex of the skull showed a small area of erosion microscopical examination of which showed well formed colloid containing thyroid vesicles No other skeletal metastases were found

(b) Blood borne metastases

In a high proportion about three quarters of fatal cases of thyroid carcinoma metastases are present in lungs, other viscera or bones The source of haemic dissemination is often demonstrable veins invaded by growth can frequently be found microscopically in the primary tumours especially in malignant adenomas or their capsules (Ehrhardt Erdheim Graham Warren Dunhill) Sometimes the tumours grow massively into large thyroid veins and extend into the jugular and innominate veins and even into the right atrium (Carrington, Shepherd, Wylegschanin) Malignant adenomas metastasize principally by

kinds of heterotopic tissues, these are teratomas (see Chapter 61). It is probable that in Zahn's first case (cited by Funkenstein) the tumour was teratomatous and not related to the tumours just discussed, for it contained not only cartilage and glandular tissue but striated muscle fibres also, and it was found in a 7 months foetus.

REFERENCES

- BEIL, F. G. (1924) Structural variations in thyroid metastases in bone with reference to benign metastatic goitre. *Brit J Surg* 12 331 (An excellent well illustrated account)
- BERARD, L., and DUNTT, C. (1921) Le goitre metastatique existe-t-il? *Rev Chir*, 59 521 (A good critical review)
- Carrington R. E. (1886) *Trans Path Soc Lond* 37, 508
- Chavannaz G. and Nadal P. (1911) *Rev Chir* 43, 317
- Cohnheim J. (1876) *Virchows Arch* 68 547
- Cole W. H. Slaughter D. P. and Rossiter L. J. (1945) *J Amer Med Assoc* 127 883
- Connell W. K. (1930) *Brit J Surg* 17, 523
- Cooray G. H. (1944) *Indian J Med Res* 32 71
- Crile G. (1939) *Surg Gyn Obst* 69 39
- Davis D. J. (1938) *Arch Path* 26 339
- DUNHILL, T. P. (1931) Carcinoma of the thyroid gland. *Brit J Surg* 19 83 (A valuable, well illustrated clinico-pathological outline)
- Ehrhardt O. (1902) *Beitr klin Chir* 35 343
- Eiselsberg, A. (1893 and 1894) *Arch klin Chir* 1893 46 430, 1894 48 489
- ERDMANN, S. (1921) Anatomische und klinische Untersuchungen über Primärgeschwülste vortauschende Metastasen insonderheit solcher des Adenocarcinoms der Schilddrüse. *Arch klin Chir* 117 274 (An excellent account with good figures and many references)
- Ewald O. (1915) *Z Krebsforsch* 15 85
- Feldman W. H. (1932) *Neoplasms of Domesticated Animals* Philadelphia
- Frantz V. K. Forsythe R. Hanford J. M., and Rogers W. M. (1942) *Ann Surg* 115 161
- Friedell M. T. (1941) *Arch Surg*, 43 386
- Funkenstein O. (1903) *Virchows Arch* 171 34
- Gierke E. (1902) *Virchows Arch* 170 464
- Graham A. (1924) *Surg Gyn Obst* 39, 781
- Graham A. (1925) *Ann Surg* 82 30
- Haagensen C. D. (1931) *Amer J Cancer* 15 2063
- Halbron P. (1904) *Bull Mém Soc Anat Paris* 79 373
- Hellwig C. A. (1935) *Amer J Cancer* 23 550
- Joff C. A. (1923) *Brit J Surg*, 11 38
- JOLL, C. A. (1932) *Diseases of the Thyroid Gland* London (Includes good well illustrated accounts of benign and malignant tumours)
- KING W. L. M., and PENIBERTON, J. (1942) So-called lateral aberrant thyroid tumors. *Surg Gyn Obst* 74 991 (An excellent critical review)
- Langhans I. (1907) *Virchows Arch* 189 69
- Marine D. (1912) *J Med Res* 27 229
- Martin J. D. and Elkin D. C. (1939) *Ann Surg* 110 169
- Nicholson G. W. (1923) *Gen s Hosp Rep* 73 298
- Nonidez J. F. (1933) *Anat Rec* 56 131
- Pick G. T., and Le Fevre R. G. (1930) *J Cancer Res* 14 167
- Pemberton J. J. (1939) *Surg Gyn Obst* 69 417
- Quinland W. S. and Cuff J. R. (1940) *Arch Path*, 30 393
- Rhea L. J. (1926) *Arch Path* 2 293
- Rosenthal D. B. and Willis R. A. (1930) *J Coll Surg Austral* 3 290
- Rudduck H. B. and Willis R. A. (1938) *Amer J Cancer* 33 205
- Shepherd F. J. (1913) *Ann Surg* 58 109
- SIMPSON W. M. (1926) Three cases of thyroid metastasis to bones with a discussion as to the existence of the so-called benign metastasizing goitre. *Surg Gyn Obst* 42 489

Zahn's and Pick's cases metastatic growths consisted of sarcomatous tissues only and were devoid of epithelial elements. Ewald reviewing 80 malignant tumours of the thyroid in dogs found 7 mixed tumours. Chavannaz and Nadal concluded that the thyroid epithelium in these growths is truly neoplastic and that the malignancy of the tumours is total involving all components. The findings in a dog tumour which Rudduck and I reported (Figs 301 and 302) supported this view for an invaded large vein contained both osteosarcomatous and epithelial components of the growth. That the former was the more actively

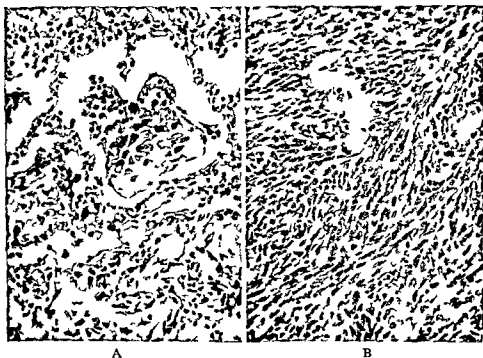


FIG 302—From pulmonary metastases of the tumour of Fig 301. A = osteosarcoma with plentiful osteoid tissue extending within lung alveoli. B = spindle-cell sarcoma with a focus of early osteoid differentiation ($\times 240$)

malignant tissue however was shown by the fact that multiple metastases in the lungs consisted of it alone without any epithelial elements as in the case of Funkenstein and others. As far as I know no case has yet been reported in which metastases have been of mixed structure thereby proving beyond doubt the total malignancy of the tumours. Specimens of mixed tumour deserve still more thorough study in order to settle this point and in any occurring in dogs or other animals an attempt to transplant the tumours and to segregate their components might lead to informative results just as it has done with the mammary mixed tumours of rats.

The osteosarcomatous or chondrosarcomatous mixed tumours of the thyroid appear to form a distinct and peculiar group arising in goitrous adult glands and associated with hyperplastic or neoplastic thyroid epithelium. Unrelated to these are some other reported mixed tumours of the thyroid containing other

CHAPTER 37

EPITHELIAL TUMOURS OF THE THYMUS

INTRODUCTION

CONFUSION still prevails regarding the nature and classification of thymic tumours, the reasons being mainly two, namely (a) doubts in the minds of some writers regarding the origin of the small thymic cells, whether these are immigrant lymphocytes or special cells derived from the thymic epithelial reticulum, and (b) the great number of mistaken diagnoses of 'thymic tumour' in cases of pulmonary and other non thymic growths with anterior mediastinal extensions. Brief discussion of these two sources of confusion is called for.

(1) The histogenesis of the small cells of the thymus

Is the small thymic cell a lymphocyte or an epithelial derivative? If the former, then we must clearly distinguish between lymphoid tumours and epithelial tumours of the thymus. If the latter, then the so called lymphoid tumours ('lympho sarcomas', etc.) of the thymus are not lymphoid at all and the round celled and epithelial celled growths are akin and can all be grouped together as "thymomas". In my opinion, the study of thymic tumours confirms the opinion of most embryologists and histologists and shows conclusively that the small round cells are lymphocytes intimately admixed with the epithelial reticulum of the organ or its tumours. The tumours show all degrees of such admixture, and all degrees of segregation of the two components. The term "thymoma" is only a means of escape from the practical difficulty of distinguishing microscopically between the more cellular diffuse lymphocyte-containing carcinomas and the relatively rare true lymphosarcomas of the organ.

The thymus is of course not the only organ the tumours of which have presented this difficulty—so also have some of those of the tonsil and other parts of the pharynx, organs to which the thymus is closely related developmentally. From all of these, arise carcinomas characterized by an abundant admixture of lymphocytes with loosely textured or diffuse epithelial growth—the so called "lympho epitheliomas". The lymphocyte rich thymic carcinomas are identical in structure and behaviour with their nasal and pharyngeal counterparts. Hence, in theory at least, we must distinguish sharply between true lymphoid tumours whether arising from thymic lymphocytes or from neighbouring lymph glands, and carcinomas arising from the thymic epithelial reticulum. In practice this may sometimes be difficult—an occasional highly anaplastic lymphocyte rich "lympho epithelioma" may easily be mistaken for a lymphoid tumour. In general diagnoses of thymic 'sarcoma' are probably about as reliable as those of pharyngeal 'sarcoma'. Many growths which were once called "lymphosarcomas" of the tonsil or pharynx are now recognized correctly as anaplastic carcinomas of lympho epithelioma type. From a perusal of the literature, there is no doubt that the same mistake has frequently been and is still being made regarding thymic tumours, many of the supposed "sarcomas" are really

- Smith L W Pool E H and Olcott C T (1934) *Amer J Cancer* 20 1
- Strachan A S (1934) *J Path Bact* 39 209
- Symmers D (1941) *Arch Path* 31 99
- Tebbutt A H and Woodhill V R (1927) *Med J Austral* ii 349
- Vaux D M (1937) *J Path Bact* 44 463
- Wapshaw H (1942) *Brit J Surg* 30 160
- Warren S (1931) *Arch Path* 11 255
- WEGELIN C (1928) Malignant disease of the thyroid gland and its relations to goitre in man and animals *Cancer Rev* 3 297
- Wilensky A O and Kaufman P A (1938) *Surg Gyn Obst* 66 1
- Willis R A (1934) *The Spread of Tumours in the Human Body* London
- Willis R A (1941) *Med J Austral* ii 258
- Wylegschanin N J (1930) *Frankfurt Z Path* 40 51

(3) Thymic tumours in animals

Curtis *et al* recorded a high incidence of thymic tumours in a colony of rats, the tumours occurred in only one strain of animals, affected females more often than males, and were usually benign but sometimes malignant. Ratcliffe also observed thymic tumours in rats. Feldman saw a carcinoma of the thymus in a ewe, and Orr saw one in a rabbit.

PERSONALLY STUDIED CASES OF THYMIC EPITHELIAL TUMOURS

I have studied 3 necropsy cases of thymic tumour in which the diagnosis is established beyond doubt. These serve to show the range of structure and behaviour of this group of tumours.

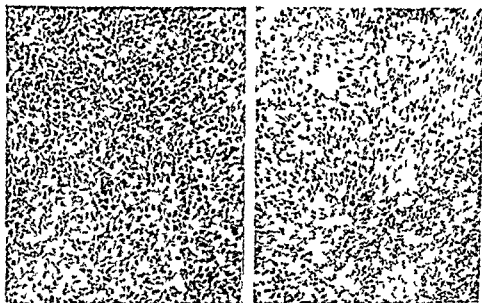


FIG 303—Case I Diffuse thymic carcinoma with many admixed lymphocytes ($\times 100$)

Case I—A female infant aged 1 year had shown recent general debility and anaemia with enlarged spleen and enlarged cervical, axillary and inguinal lymph glands. Blood examination excluded leukaemia. *Necropsy*—Large thymic tumour (70 grammes) enlargement of many groups of lymph glands by tumour deposits; diffuse and nodular tumour infiltration of spleen (310 grammes). All other viscera and bone marrow free from growth. *Histology* (Fig 303)—Growths in thymus glands and spleen all show similar structure consisting of large polyhedral and irregular epithelial cells of diffuse reticular arrangement with some poorly formed whorls with many mitotic figures; patchy infiltrations of lymphocytes partly focal and partly diffuse; mingled with the epithelial reticulum throughout; large areas of necrosis present in places. *Comment*—In briefly recording this case previously (Willis 1934) although I classified it provisionally as a thymic carcinoma with metastases I suggested also the possibility of its being some kind of systemic neoplasia affecting thymus glands and spleen simultaneously. Further study in the light of other published cases however fully convinces me that the tumour was indeed a thymic carcinoma.

Case II—History—In October 1936 a man aged 47 professional athlete, was admitted to hospital because of severe left precordial and epigastric pain of 6 days' duration worse on exertion and accompanied by dyspnoea. Skiagrams showed right basal pleural effusion and enlargement of heart shadow with a large oval projection on

diffusely cellular carcinomas with admixed lymphocytes and genuine primary lymphosarcoma and other sarcomas of the thymus are very rare

(2) Mistaken diagnoses of ' thymic tumour '

This second cause of error is even more serious than the first. It cannot be too strongly insisted that the diagnosis of thymic carcinoma can be made with confidence only when careful necropsy examination has excluded the possibility of the mediastinal mass being secondary to some other growth. This obvious requirement has so often been ignored, that many otherwise carefully recorded series are rendered valueless for analysis of the properties of thymic growths. For example Symmers recorded that in 10 of his 25 supposedly thymic tumours ' the larger bronchi were buried in tumor tissue ' and that in many cases the bronchial walls were infiltrated and their lumina encroached on. So also Parabutschew, though insisting that the diagnosis of thymic carcinoma necessitated exclusion of the possibility of a primary tumour elsewhere reported as thymic in origin two cases (his second and fourth) in which the lungs were extensively involved and might easily have been the primary source of the growths. Crosby's tabular summary of recorded cases of thymic tumour shows how frequently the lungs are reported to have been involved secondarily and direct reference to many of these cases confirms the suspicion that the primary source and direction of spread may well have been misinterpreted.

Clearly, of course malignant thymic growths *are* likely to invade the lungs and it is not intended to deny that some of the recorded tumours with extensive involvement of the lungs may indeed have been thymic in origin. But clearly, involvement of the lungs necessarily introduces room for doubt regarding the primary source of the tumour and the more extensive this is and the more closely it is related to bronchi the greater is the probability of a pulmonary origin. Pulmonary tumours are much commoner than thymic ones they often produce massive lymph nodal or mediastinal extensions and these can arise from very small elusive primary growths (see Chapter 19).

It may be argued that microscopical study should enable us to distinguish thymic from pulmonary and other carcinomas. Certainly some thymic growths have a rather distinctive lympho epithelial structure and this may sometimes afford good evidence of the source of a tumour of otherwise doubtful origin. But great experience and caution will be needed in making such a differential microscopical diagnosis and the number of tumours in which it will be possible to do so must be small. In most cases confident microscopical distinction between thymic carcinoma and poorly differentiated epidermoid or other anaplastic carcinomas of the lungs will not be possible.

For the foregoing reasons many of the recorded cases of ' thymic carcinoma (or thymic sarcoma) are suspect even though some of them may have been genuine enough. Hence no trustworthy analysis of age or sex incidence or other properties is at present possible. The number of unimpeachable cases so far recorded is too few to permit generalizations. For useful accounts and references, see Parabutschew Margolis Crosby and Wu. (The thymic tumours associated with myasthenia gravis or with endocrine disturbances are referred to separately below)

EPITHELIAL TUMOURS OF THE THYMUS

4th and 9th dorsal and the 3rd and 4th lumbar vertebrae contained some irregular areas of soft white or mottled growth. Naked-eye necropsy diagnosis was ' ? cystic anterior

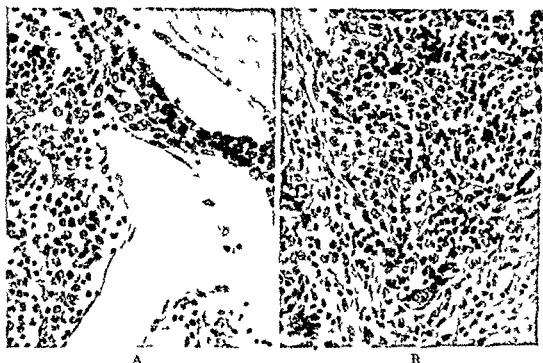


FIG 305—Case II Structure of carcinoma A — well defined epithelial clumps containing scattered lymphocytes B = diffusely mixed carcinoma and lymphoid cells ($\times 300$)



FIG 306—Case III Typically epithelial growth with whorls and scattered lymphocytes ($\times 120$)

mediastinal teratoma old teratomatous metastases in left pleura recent malignant degeneration with metastasis to lymph glands liver and bones Histology (Figs 304 and 305) —The cavities in the mediastinal and pleural tumours are lined irregularly by

its right border—? neoplasm Discharged improved in December he was readmitted in January 1937 because of another similar attack no noteworthy changes in physical signs or radiographic appearances diagnosis coronary occlusion again discharged improved Patient then remained well until August 1940 when he had an attack of pneumonia In October he began to suffer from pains in neck chest and left arm and from increasing dyspnoea hoarseness and feeling of pressure in chest Admitted to hospital in February 1941 he was found to have visible anterior bulging of upper part of sternum a large area of dullness to percussion enlarged superficial veins and right basal dullness Skiagrams showed large anterior mediastinal tumour and several well defined globular shadows in left lung field—? metastatic tumours—? hydatids Died in March 1941 *Necropsy*—Anterior mediastinum occupied by large well defined roughly



FIG 304—Case II Cystic carcinomatous masses separated by thick densely fibrous septa ($\times 80$)

wedge-shaped but lobulated mass 12 centimetres in transverse diameter 10 centimetres vertically and 4 centimetres in maximal thickness at its upper end displacing sternum forward overlapping both lungs and basal half of pericardium which were adherent to but not invaded by the growth This was very hard and on section consisted of small and large irregular cavities up to 3 centimetres in diameter lined only here and there by a thin layer of white tumour tissue and occupied mainly by fibrous material or blood stained fluid and separated by thick irregular partly calcified partitions continuous with the main capsule of the growth A bulging lobule of the growth projected towards the hilum of the right lung but without invasion of lung tissue All bronchi normal Left pleural cavity contained 5 discrete well-defined encapsulated hard cystic masses similar in structure to main growth situated as follows (a) at apex a discoid mass 10 centimetres in main diameter adherent to apex of lung upper ribs and deep tissues of neck (b) rounded tumour 9 centimetres in diameter in lower lateral part of pleural cavity (c) a smaller rounded tumour close to preceding one (d) interlobar in position (e) between base of lung and diaphragm Lymph glands near angle of trachea were enlarged and contained soft white growth unlike that of the thymic and pleural tumours Liver contained several small scattered soft white or greyish metastases the largest 2 centimetres in diameter All other lymph glands viscera and brain were carefully examined and no growths found A small peptic ulcer was present in the stomach a healed scar in the duodenum and adrenals showed some nodular cortical hyperplasia The dura and bone of the right border of the foramen magnum presented a projecting mass of soft greyish tumour The

tissue admixed with lymphocytes, the epithelium being most disorderly and diffuse in Case I and most compact and well differentiated in Case III. The three tumours are in fact "lympho epitheliomas" of descending order of anaplasia and malignancy. The structural variations displayed show clearly that the epithelium is the essential tumour parenchyma and that the lymphocytes are immigrants unrelated genetically to it. The lymphocytes are of patchy distribution, of very variable proportions in different parts of the growths, and often most plentiful in perivascular tissues as if they had collected in the tumours in response to some lymphocyte-attracting property of the epithelium, a property which we would expect to vary from part to part of a tumour according to the differentiation and growth properties of its cells. The absence of cornification in the three tumours is noteworthy, this accords with the findings of most other workers, squamoid characters in the tumours are often restricted to the formation of cell whorls or groups of cells resembling Hassall's corpuscles. Case II strikingly exemplifies both the cystic tendency of thymic carcinoma, and the great stromal proliferation which the more chronic forms of growth induce.

(2) Behaviour

Cases I and II exemplify metastasis both to lymph glands and by the blood stream to remote viscera and bones. In addition, Case II illustrates the slow progress of some thymic carcinomas, and also the unusual phenomenon of trans pleural transplantation of a very chronic tumour. Danisch and Nedelmann saw a thymic tumour in a child of 3½ years the structure of which resembled that of my Case I but with a higher proportion of lymphocytes, and which invaded the innominate vein and metastasized widely to the choroid plexus, meninges, heart wall and kidneys, as well as to the cervical lymph glands. The absence of invasiveness or metastasis in my Case III leads us to a brief discussion of the thymic tumours associated with myasthenia gravis.

THYMIC TUMOURS IN MYASTHENIA GRAVIS

Thymic enlargement in myasthenia gravis was first described by Carl Weigert in 1901 (cited by Blalock *et al*, 1939). In 1917, Bell collected 56 records of cases of myasthenia gravis in which necropsy or operation had been performed, 27 of these had thymic abnormalities, described as tumours in 10 cases and as persistence or simple enlargement of the thymus in the remainder. Norris (1936 and 1937) and Blalock *et al* (1939 and 1941) have reviewed later records. Norris at first inclined to the view that the lesion was hyperplastic only and not a true tumour, but later modified this opinion and concluded that it was an "adenoma". The size and structure of the growth in some reported cases (as my Case III) indicate true tumours, but in other cases (e.g. those of Blalock *et al* 1941) there has been simple enlargement only. All of the tumours reported have been benign. No definite case of associated carcinoma of the thymus and myasthenia has been reported. The beneficial effect on the myasthenia of removal of the tumour has been well established, but the precise relationship of the two still remains obscure.

THYMIC TUMOURS AND ENDOCRINE DISTURBANCES

Although there is no clear evidence that the thymus produces an internal

compact or loosely reticular epithelium of stratified type but without cell nests or cornification mitoses few. Plentiful lymphocytes mingle with the epithelium in varying proportions. The ramifying epithelial masses and cysts are embedded in and separated by bulky densely fibrous septa in which much calcification and some ossification have taken place. Metastases in lymph glands liver and bones show spheroidal-cell carcinoma with many mitoses lymphocytic infiltration though present in parts is much less abundant than in the thymic and pleural tumours. *Diagnosis and comment*—The histology establishes the diagnosis of thymic carcinoma of lympho epithelial type the neoplastic epithelium is similar to that of many pharyngeal tumours. Remarkable are the long duration (at least 4½ years probably much longer) the extreme cystic change in the older growths the great stromal fibrosis evoked by these the metaplastic ossification of stroma and the two distinct kinds of metastases namely those in the left pleura of the slowly growing cystic type with great stromal reaction as in the primary growth and those in the viscera of active carcinomatous structure and clearly of recent development. Doubtless



FIG 307—Case III Details of epithelial whorls seen in Fig 306 ($\times 250$)

the sudden severe but evanescent attacks of thoracic pain in 1936 were due to rupture of part of the cystic thymic tumour into the left pleural cavity whence arose the peculiar unilateral metastases of relatively benign type like the parent tumour. The more recent dissemination to viscera and bones must be attributed to an exacerbation of growth rate and malignancy in some part of the primary growth.

Case III—Necropsy (Dr E H Derrick) on an emaciated man of 39 years who had had symptoms of myasthenia gravis for some years disclosed a firm well-defined nodular thymic tumour $5 \times 5 \times 2.5$ centimetres weighing 34 grammes composed of grey or haemorrhagic tissue with spongy finely cystic areas enclosed in fibrous capsule and trabeculae. *Histology* (Figs 306 and 307)—Bulk of tumour is composed of large masses of epithelium separated by vascular fibrous stroma. Epithelium is of stratified type and contains some small whorls but shows no cornification. Most of it is compact but other parts are loosely reticular or contain many small spaces. Mitoses in tumour cells are very few. Infiltrations of lymphocytes are present in all parts most plentiful in the perivascular stromal tissue and mingled with the reticular areas of epithelium.

COMMENTS ON FOREGOING CASES

(1) Structure

The three tumours have this in common—they all consist of an epithelial

CHAPTER 38

EPITHELIAL PITUITARY AND PARAPITUITARY TUMOURS

EPITHELIAL tumours of the pituitary gland and of the developmental residues associated with it can be conveniently grouped as follows

Group 1 Tumours of the secreting tissue proper

- 1 Benign adenomas
 - (a) Chromophobe
 - (b) Eosinophil
 - (c) Basophil
 - (d) Mixed
- 2 Carcinomas

Group 2 Tumours of the parapituitary residues

- 1 Simple cysts
- 2 Squamous cell carcinomas and "adamantinomas"

Good general accounts with many references, include those of Strada (1911) and Erdheim (1925). Cushing's monograph (1912) and Dott and Bailey's paper (1926) are major contributions to the subject. Biggart and Dott (1936) have given a useful brief summary.

PITUITARY ADENOMAS

The non invasive tumours of the pituitary secretory tissues are all appropriately called adenomas. Their structure and their all but constant intrasellar situation show that most of them arise from the anterior lobe, but though difficult to prove, it is probable that occasional tumours may arise from the epithelium of the pars intermedia or of the pars tuberalis. According to the staining properties of their cells, three main types of adenomas are distinguished—chromophobe, eosinophil and basophil, but this distinction is somewhat arbitrary, since tumours of mixed type occur. Pituitary adenomas occur mainly in young and middle aged adults, they rarely appear in patients under 20 years of age or in the elderly.

(1) Chromophobe adenoma

This group comprising about two thirds of all pituitary adenomas, includes all adenomas the cells of which show non distinctive staining properties. The growths are of very diverse structure. Some of them consist of trabeculae of polyhedral cells with intervening stroma and vessels, closely simulating the general structure of the normal gland. Others depart from this in various ways, presenting reticular patterns, prominent perivascular mantles of cells, elongated cells, or areas of pale cells with vacuolated cytoplasm. Elsewhere (1938) I have depicted examples of these variations, and have stressed the structural diversity of the group. Mitoses are infrequent, but no sharp separation can be made between the common benign tumours and the rarer malignant ones showing anaplasia and invasiveness.

secretion certain pathological observations suggest some relationship of thymic and endocrine functions. On the one hand thyrotoxicosis is often accompanied by thymic enlargement and on the other hand rare cases of thymic tumour or enlargement have shown marked endocrine disturbances. Thus Leyton *et al* fully described the necropsy findings in two patients with thymic tumours, one in a boy of 11 years who had had hirsutism and diabetes, the other in a man of 31 with adiposity and diabetes both cases showed also enlargement of the thyroid and adrenal cortex. Duguid and Kennedy saw a thymic tumour accompanied by similar endocrine disturbances in a woman of 64. Parkes Weber described a case of precocious muscular and sexual development in a boy who had also an extensive unilateral pigmented naevus and X ray evidence of marked thymic enlargement later, however, this boy developed normally, and the enlarged thymic shadow in skiagrams disappeared.

REFERENCES

- Bell, E. T. (1917) *J Nerv Mental Dis* 45 130
Blalock A. Harvey, A. M. Ford F. R. and Lilienthal J. L. (1941) *J Amer Med Assoc* 117 1529
BLALOCK, A. MASON M. F., MORGAN H. J. and RIVEN S. S. (1939) Myasthenia gravis and tumors of the thymic region *Ann Surg* 110 544 (A useful review)
Crosby E. H. (1932) *Amer J Cancer* 16 461
Curtis M. R. Bullock F. D. and Dunning W. F. (1931) *Amer J Cancer* 15 67
Danisch F. and Nedelmann E. (1928) *Virchows Arch* 268 492
Duguid J. B. and Kennedy A. M. (1930) *J Path Bact* 33 93
Feldman W. H. (1931) *Amer J Cancer* 15 2044
LEYTON O. TURNBULL, H. M. and BRATTON, A. B. (1931) Primary cancer of the thymus with pluri glandular disturbance *J Path Bact* 34 635 (Detailed study of two remarkable cases)
Margois H. M. (1931) *Amer J Cancer* 15 2106
Norris E. H. (1936 1937) *Amer J Cancer* 1936 27 421 1937 30 308
Orr J. W. (1939) *Amer J Cancer* 35 269
Parabutechew A. (1930) *Z Krebsforsch* 30 380
Ratchiffe H. L. (1940) *Amer J Path* 16 237
Symmers D. (1932) *Ann Surg* 95 544
Weber F. P. (1946) *Rare Diseases* p 82 London
Willis R. A. (1934) *The Spread of Tumours in the Human Body* p 436 London
Wu T. T. (1935) *J Path Bact* 41 351

and 1933) that these growths were the essential cause of a syndrome which he designated "pituitary basophilism" and which is often referred to as "Cushing's syndrome", is now untenable. The syndrome itself is very variable and often imperfectly manifested by patients with basophil adenomas (Russell *et al.*), and identical syndromes are found in patients with adrenal cortical tumours and without pituitary adenomas (references in Chapter 39). Hence, while it is true that basophil adenomas of the pituitary are found in many cases showing the symptoms of Cushing's syndrome, all of these symptoms cannot be directly attributed to hypersecretion of basophil cells. It is probable that the condition is a polyglandular disturbance in which both pituitary and adrenal glands are implicated. Further careful necropsy and experimental work is needed to determine which of the many and variable symptoms included in the syndrome are related to pituitary dysfunction and which to dysfunction of the adrenal cortex or other ductless glands.

(4) Growth and behaviour of pituitary adenomas

Most pituitary adenomas grow slowly and non-invasively. In their early stages they are often not encapsulated, and it is probable that they commence as focal hyperplasias which go on to tumour formation, a sequence similar to that observed more clearly in the thyroid gland. Since adenomas are with rare exceptions intrasellar growths they usually cause early enlargement of the pituitary fossa and early compression and hypofunction of the remainder of the gland. Bulky tumours expand and project through the diaphragma sellae into the cranial cavity where they compress the optic chiasma and tracts, indent the hypothalamic region or mid brain, fill and distend the third ventricle, and even extend through the foramina of Monro into the lateral ventricles. They may also project into and distend the sphenoidal and nasal cavities. Large tumours often show cystic and degenerative changes. Striking examples of expansive extension will be found in Strada's, Erdheim's and Cushing and Davidoff's studies. Invasive growth or metastasis places the tumour in the malignant group now to be discussed.

CARCINOMAS OF PITUITARY GLANDULAR TISSUE

Some pituitary tumours must be classified as malignant because of local invasive spread or, more rarely, metastasis by the cerebrospinal fluid or blood stream. But these tumours are not sharply separable from the common non-invasive adenomas; they are merely more aggressive members of the same species.

(1) Anaplasia and invasive spread

When a pituitary tumour invades the neighbouring dura, bones and sphenoidal sinus, as in two cases which I reported in 1938, it may be difficult or impossible to be sure that the growths are indeed of pituitary origin and have not arisen in the sinus or other neighbouring parts. However the whole of the evidence pointed to a pituitary origin in my two cases, and indubitable instances have been described also by Strada, Dott and Bailey and others. One of my specimens from a girl of 14, showed a seminoma-like structure with ill-defined groups of large spheroidal

and plentiful mitoses (*see below*) Chromophobe adenomas produce no symptoms attributable to secretory activity of the tumour cells their usual endocrine results are due to diminished pituitary functions or to compression of neighbouring structures They often attain a large size

(2) Eosinophil adenoma

Tumours consisting wholly or partly of eosinophil cells with characteristic granules and producing excessive growth hormone constitute about one third of the pituitary adenomas Acromegaly or acromegalic gigantism is probably always due to eosinophil adenoma and predominantly eosinophil cell adenomas always produce acromegaly Predominantly chromophobe cell tumours may however, contain a few eosinophil cells without producing obvious acromegalic changes

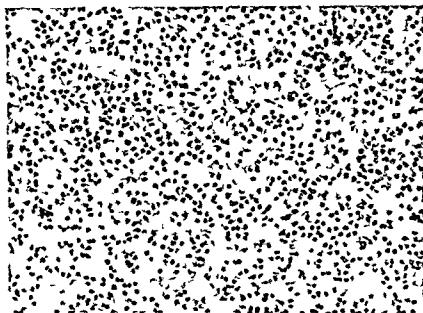


FIG 308 —Pituitary adenoma composed entirely of eosinophil cells from a man aged 42 with advanced acromegaly ($\times 180$)

It is clear that eosinophil and chromophobe adenomas are not sharply distinct types but merely variants of the one kind of tumour with greater or lesser degrees of cellular differentiation and production of growth hormone Microscopically most of the eosinophil cell growths show a general structure closely similar to that of the normal tissue and with varying proportions of eosinophil cells in some cases all of the cells are eosinophil (Fig 308) The tumours sometimes attain a large size but on the average they are smaller than chromophobe adenomas For the clinical and pathological changes of acromegaly and gigantism *see* Cushing and Davidoff Knaggs and Laurie

(3) Basophil adenoma

Basophil cell adenomas are rare and small seldom exceeding a few millimetres in diameter and sometimes being almost microscopic Biggart and Dott mention having seen a specimen 2 centimetres in diameter Cushing's original view (1932

body of the sphenoid, in the capsule of the pituitary gland especially of its anterior lobe, in the pars intermedia and around the infundibulum. The "pharyngeal pituitary gland" which is present in nearly all subjects (Haberfeld, Christeller, Melchionna and Moore), and the occasional epithelial residues in the body of the sphenoid, are rarely the site of tumours. But the abundant residues in the pituitary capsule and infundibulum, found in about one third of adults (Carmichael, Susman), not infrequently give origin to cysts and tumours, which have often been lumped together under the unsatisfactory name "craniopharyngioma". Most of these cysts and tumours arise from the suprasellar residues, but some arise from those within the pituitary fossa. For good accounts see Critchley and Ironside, Erdheim, Frazier and Alpers (1931) and Frazier.

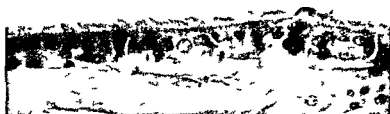


FIG. 310.—Wall of a pituitary cyst lined by ciliated epithelium found at necropsy on a woman aged 29 with Frohlich's syndrome ($\times 450$)

(1) Simple cysts of the parapituitary residues

These need not concern us in detail here. They are usually lined by squamous stratified epithelium, in contradistinction to intrapituitary cysts lined by columnar ciliated epithelium (Fig. 310), which are believed to arise from Rathke's cleft in the pars intermedia (Frazier and Alpers, 1934; Frazier, 1936).

(2) Tumours of the parapituitary residues

There occur slowly growing squamous cell carcinomas and "adamantinomas". These are not distinct kinds of growth, and the improper term "adamantinoma" means no more than that tumours of the parapituitary residues often closely resemble in structure those of the parodontal residues. (Compare Figs. 311 and 312 with Figs. 130–132 of Chapter 16.) This resemblance is not surprising considering that both sets of residues have a closely similar developmental origin and consist of closely similar foci of indifferent epithelium. Like their parodontal counterparts also parapituitary "adamantinomas" occur in relatively young subjects. Of 18 cases described and reviewed by Critchley and Ironside, 7 were in the second decade and 6 in the third, the youngest patient was 7, and the oldest 60 years. Of 14 cases studied by Frazier and Alpers, 9 were between the ages of 7 and 17 and the ages of the remaining 5 patients were 25, 28, 33, 38 and 50. I have examined 4 specimens of parapituitary "adamantinoma" from patients aged 10, 14, 24 and 28. One of these, from Case XIX of my 1938 paper, is depicted in Figs. 311 and 312. These slowly growing tumours are often cystic and calcified,

tumour cells with many mitoses accompanied by scanty stroma with collections of lymphocytes (Fig 309)

(2) Cerebrospinal metastasis

Cerebrospinal dissemination of a pituitary tumour was recorded by Cagnetto, although the necropsy was incomplete, this interpretation was probably correct. Cairns and Russell briefly mentioned a case of bulky pituitary adenoma in which peculiar cells had been observed in the cerebrospinal fluid during life and in which necropsy revealed scattered cells in the spinal meninges but without gross tumour formation.



FIG 309 — Anaplastic seminoma like malignant pituitary tumour from a girl aged 14 (*reported in 1938*) ($\times 85$)

(3) Blood borne metastases

These are very rare. Budde's case of spheroidal-cell carcinoma with metastases in cervical lymph glands, lungs and pleura was probably but not certainly of pituitary origin. Dott and Bailey mentioned a necropsy case of pituitary carcinoma with metastases in liver and lymph gland but gave no details. Vasilu's diagnosis of primary pituitary tumour in a case showing a large mediastinal growth and many metastases in bones cannot be accepted; it is much more likely that the small pituitary tumour was metastatic and that a primary carcinoma of the lung escaped detection. Similarly Gilmour's case of carcinoma of the pituitary gland with abdominal metastases was more probably one of primary abdominal—perhaps renal—carcinoma with a pituitary metastasis. Forbes has reported a convincing specimen of carcinoma of the anterior pituitary lobe with metastases in the liver.

THE PARAPITUITARY RESIDUES AND THEIR TUMOURS

Small foci of squamous celled or nondescript epithelium derived from the stalk of Rathke's pouch are found in the adult in the roof of the nasopharynx, in the

PITUITARY AND PARAPITUITARY TUMOURS IN ANIMALS

Hare described a chromophobe adenoma associated with dystrophia adiposogenitalis in a bitch aged 9 years, and referred to two previous reports of adenomas in horses. White reported a peculiar squamous-cell cystic suprasellar tumour in a male dog of 4 years. Great enlargements of the pituitary gland can be produced in rats or mice by prolonged treatment with oestrogens (see Section V, Chapter 4) but it is doubtful if these are true neoplasms, since there is as yet no evidence that they progress after cessation of the treatment. Vasquez-Lopez, however, has succeeded in producing large atypical growths with all the appearances of true tumours, by a combination of oestrogen treatment and the administration of either thiourea or acetylaminofluorene.

REFERENCES

- Biggart J H and Dott N M (1936) *Brit Med J* **ii** 1153
 Budde M (1921) *Frankfurt Z Path* **25** 16
 Cagnetto G (1904) *Virchows Arch* **176** 115
 Cairns H and Russell D (1931) *Brain* **54** 377
 Carmichael H T (1931) *Arch Neurol Psych* **26** 966
 Christeller E (1914) *Virchows Arch* **218** 185
 CRITCHLEY, M and IRONSIDE, R N (1926) The pituitary adamantinomatous, *Brain*, **49** 437 (Good reports of 7 cases)
 CUSHING, H (1912) *The Pituitary Body and its Disorders* Philadelphia
 CUSHING, H, and DAVIDOFF, L M (1927) The pathological findings in four autopsied cases of acromegaly. *Monographs of Rockefeller Institute of Medical Research* No 22
 Cushing H (1932) *Bull Johns Hopkins Hosp* **50** 137
 Cushing, H (1933) *Arch Int Med* **51** 487
 DOTT, N M, and BAILEY, P (1926) A consideration of the hypophysial adenomata, *Brit J Surg* **13** 314
 ERDHEIM, J (1925) Pathologie der Hypophysengeschwulste. *Ergeb allgem Path* Part I **21** 482 (A valuable well illustrated account epitomizing the writer's own researches and containing a full list of references)
 Forbes W To appear in *J Path Bact*
 Frazier C H and Alpers, B J (1931) *Arch Neurol Psych* **26** 905
 Frazier C H and Alpers B J (1934) *Ibid* **32** 973
 FRAZIER, C H (1936) 'A review clinical and pathological or parahypophyseal lesions', *Surg Gyn Obst* **62** 1
 Garsch W (1930) *Z Krebsforsch* **31** 432
 Gilmour M D (1932) *J Path Bact* **35** 265
 HABERFELD W (1909) Die Rachendachhypophyse andere Hypophysengangreste und deren Bedeutung für die Pathologie. *Beitr path Anat* **46** 133
 HABERFELD, W (1910) Zur Pathologie des Canalis craniopharyngeus. *Frankfurt Z Path* **4** 96
 Hare T (1932) *Proc Roy Soc Med* **25** 1493
 Joseph H (1925) *Virchows Arch* **254** 439
 KNAGGS, R L (1935) Acromegaly. *Brit J Surg* **23** 69
 Laurie H W S (1937) *Med J Austral* **i** 133
 Melchionna R H and Moore R A (1938) *Amer J Path* **14** 763
 Russell, D S Evans H and Crooke A C (1934) *Lancet* **ii** 240
 STRADA, F (1911) Beiträge zur Kenntnis der Geschwulste der Hypophyse und der Hypophysegegend. *Virchows Arch* **203** 1
 Susman W (1932) *Brit J Surg* **19** 571
 Vasilu T (1930) *Virchows Arch* **276** 141
 Vasquez Lopez E Personal communication of work yet unpublished
 White E G (1938) *J Path Bact* **47**, 323
 Willis, R A (1938) *Med J Austral* **i** 287

yet infiltrative and dangerous invading the adjacent bones or brain and frequently recurring after removal. It is not unusual for bone to develop by metaplasia in

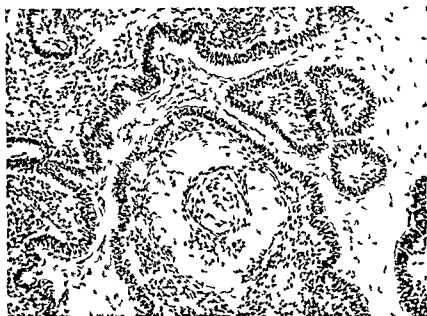


FIG 311—Pituitary adamantinoma from a girl aged 14 (*Case XIX Willis 1938*) ($\times 120$)

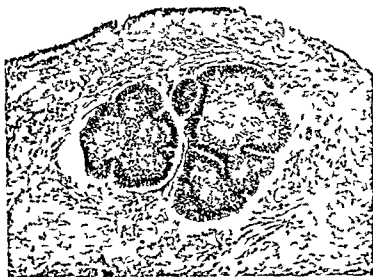


FIG 312—From the same case as Fig 311 showing tumour clumps invading nervous tissue in wall of third ventricle ($\times 85$)

the stroma of the growths (Erdheim Josephy). Metastasis occurs rarely if ever. Garschin reported a large squamous-cell carcinoma of the sphenoid and pituitary fossa which he believed possibly correctly, to have arisen from intrasphenoidal parapituitary residues, and which had metastasized to lung lymph glands and liver.

PITUITARY AND PARAPITUITARY TUMOURS IN ANIMALS

Hare described a chromophobe adenoma associated with dystrophia adiposogenitalis in a bitch aged 9 years, and referred to two previous reports of adenomas in horses. White reported a peculiar squamous cell cystic suprasellar tumour in a male dog of 4 years. Great enlargements of the pituitary gland can be produced in rats or mice by prolonged treatment with oestrogens (see Section V, Chapter 4) but it is doubtful if these are true neoplasms, since there is as yet no evidence that they progress after cessation of the treatment. Vasquez-Lopez, however, has succeeded in producing large atypical growths with all the appearances of true tumours, by a combination of oestrogen treatment and the administration of either thiourea or acetaminofluorene.

REFERENCES

- Biggart J H and Dott N M (1936) *Brit Med J*, **ii**, 1153
 Budde M (1921) *Frankfurt Z Path* **25** 16
 Cagnetto G (1904) *Virchows Arch* **176** 115
 Cairns H and Russell D (1931) *Brain* **54** 377
 Carmichael H T (1931) *Arch Neurol Psych*, **26** 966
 Christeller E (1914) *Virchows Arch* **218** 185
 CRITCHLEY, M, and IRONSIDE, R N (1926) The pituitary adamantinoma, *Br J* **49** 437 (Good reports of 7 cases)
 CUSHING, H (1912) *The Pituitary Body and its Disorders* Philadelphia
 CUSHING, H, and DAVIDOFF, L M (1927) The pathological findings in four autopsied cases of acromegaly. *Monographs of Rockefeller Institute of Medical Research*, No 22
 Cushing H (1932) *Bull Johns Hopkins Hosp* **50**, 137
 Cushing H (1933) *Arch Int Med* **51** 487
 DOTT, N M, and BAILEY, P (1926) A consideration of the hypophysial adenomata *Brit J Surg*, **13** 314
 ERDHEIM, J (1925) Pathologie der Hypophysengeschwulste *Ergeb allgem Path* Part I **21** 482 (A valuable well illustrated account epitomizing the writer's own researches and containing a full list of references)
 Forbes W To appear in *J Path Bact*
 Frazier C H, and Alpers B J (1931) *Arch Neurol Psych*, **26** 905
 Frazier C H and Alpers B J (1934) *Ibid* **32** 973
 FRAZIER, C H (1936) A review clinical and pathological of parhypophyseal lesions *Surg Gyn Obst* **62** 1
 Garschin W (1930) *Z Krebsforsch* **31** 432
 Gilmour M D (1932) *J Path Bact* **35** 265
 HABERFET D, W (1909) Die Rachenachhypophyse andere Hypophysengangreste und deren Bedeutung für die Pathologie, *Beitr path Anat* **46** 133
 HABERFELD, W (1910) Zur Pathologie des Canalis craniopharyngeus, *Frankfurt Z Path* **4** 96
 Hare T (1932) *Proc Roy Soc Med* **25** 1493
 Josephy H (1925) *Virchows Arch* **254** 439
 KNAGGS R L (1935) Acromegaly *Brit J Surg* **23** 69
 Laurie H W S (1937) *Med J Austral* **i** 133
 Melchionna R H, and Moore R A (1938) *Amer J Path* **14** 763
 Russell D S Evans H and Crooke A C (1934) *Lancet* **ii** 240
 STRADA, F (1911) Beiträge zur Kenntnis der Geschwulste der Hypophyse und der Hypophysegegend *Virchows Arch* **203** 1
 Susman W (1932) *Brit J Surg* **19** 571
 Vasilu T (1930) *Virchows Arch* **276** 141
 Vasquez Lopez E Personal communication of work yet unpublished
 White E G (1938) *J Path Bact* **47** 323
 Willis R A (1938) *Med J Austral* **i** 287

CHAPTER 39

TUMOURS OF THE ADRENAL CORTEX

BENIGN ADENOMAS

SMALL cortical adenomas of the adrenals are frequently discovered incidentally at necropsy. They appear as well circumscribed rounded yellow masses similar in appearance to the cortex of the gland, rarely more than 2 or 3 centimetres in diameter usually single but sometimes multiple. They are found most often in middle aged or old subjects and in women more often than men and they are not associated with any distinct endocrine disturbances. In structure they closely resemble the normal cortex and usually show pronounced lipoid vacuolation of their cells (Fig 313). Metastatic tumours in the adrenal cortex show a decided predilection for adenomas (Willis 1934).

CORTICAL CARCINOMAS OR 'HYPERNEPHROMAS'

The nomenclature of the large progressively growing tumours of the adrenal cortex needs clarification. The term hypernephroma has deservedly fallen into such bad odour because of its frequent misapplication to renal tumours and also to non cortical adrenal tumours that it should be discarded. But to call the tumours carcinomas is to assert their epithelial nature while as pointed out in Chapter 2 histologists are loth to regard the adrenal cortex as epithelial. However cells of the adrenal cortex and its tumours are epithelium like in their general structure and arrangement and most pathologists think of them as epithelial. Hence I can see little real objection to applying the name carcinoma to the tumours. Again no sharp separation of benign and malignant growths is possible whether a large circumscribed but growing tumour shall be regarded as an unusually active adenoma or as a carcinoma' which has not yet displayed invasiveness or metastasis is a matter of personal preference.

Bulloch and Sequiera's paper in 1905 was the first in this country to concentrate attention on the association of adrenal cortical tumours and sexual development. In 1912 Glynn published his classical account of the subject which he amplified in 1921 in a further important paper. Proof of the endocrine activity of the tumours was afforded by improvement in the signs of virilism following surgical removal of the tumours as in the cases described by Holmes (1925) and Murray and Simpson (1927). More recent reviews and general accounts of the subject include those of Kepler, Kepler and Keating, Simpson and Joll Broster *et al* and Cahill *et al*.

(1) Age and sex incidence

No age is exempt the tumours have been found in infancy and in old age but most patients have been between 25 and 45 years of age. Females are affected much more often than males and the same sex difference is seen in pre adolescents as in adults. In 1939 Reilly *et al* found records of 40 cases in pre adolescent girls while in 1941 Kepler and Keating could find only 17 cases in boys.

(2) Structure and growth

Many of the tumours have a well differentiated structure closely resembling that of the adrenal cortex. When such tumours are well circumscribed and devoid of metastases and have not recurred after surgical removal, no objection can be raised to calling them 'adenomas'. But tumours of similar structure may recur or metastasize, and distinction between benign and malignant growths is therefore arbitrary. Other tumours, however, are frankly malignant in structure and behaviour, exhibiting varying degrees of cellular anaplasia and invasiveness, and often showing variable differentiation in different parts, some areas being adrenal cortex-like while others show disorderly cellular pleomorphism. These variations of structure are well depicted by Cahill *et al*. Special cytological details related to the hormonal properties of the tumours are discussed below.

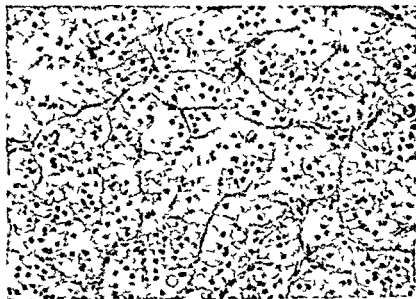


Fig. 313.—Cortical adenoma of adrenal gland: a solitary spherical tumour 2.5 centimetres in diameter from a woman aged 60 ($\times 150$).

The sizes attained by the tumours vary greatly. Some have attracted attention by their endocrine results while still quite small, others have grown to huge sizes without producing noticeable hormonal disturbances. As examples of large tumours may be mentioned the tumour of benign type accompanied by pronounced virilism removed by Holmes which weighed 1,025 grammes, and the malignant tumour accompanied by only slight hormonal upset, described by Anderson *et al*, which weighed 1,780 grammes.

Examples of fatal recurrence after removal, or metastasis to the lungs, liver or elsewhere include those of Murray and Simpson, Hare *et al*, Simpson and Joll and Anderson *et al*. In Feinblatt's case a virilizing right adrenal tumour in a woman of 32 had invaded the inferior vena cava and extended up to the heart. In Busch's case a man of 27 had gynaecomastia as the first symptom, enlarged left cervical lymph nodes appeared and biopsy of these established the diagnosis.

CHAPTER 39

TUMOURS OF THE ADRENAL CORTEX

BENIGN ADENOMAS

SMALL cortical adenomas of the adrenals are frequently discovered incidentally at necropsy. They appear as well circumscribed rounded yellow masses similar in appearance to the cortex of the gland rarely more than 2 or 3 centimetres in diameter usually single but sometimes multiple. They are found most often in middle aged or old subjects and in women more often than men and they are not associated with any distinct endocrine disturbances. In structure they closely resemble the normal cortex and usually show pronounced lipid vacuolation of their cells (Fig 313). Metastatic tumours in the adrenal cortex show a decided predilection for adenomas (Willis 1934).

CORTICAL CARCINOMAS OR 'HYPERNEPHROMAS'

The nomenclature of the large progressively growing tumours of the adrenal cortex needs clarification. The term *hypernephroma* has deservedly fallen into such bad odour because of its frequent misapplication to renal tumours and also to non cortical adrenal tumours that it should be discarded. But to call the tumours *carcinomas* is to assert their epithelial nature while, as pointed out in Chapter 2 histologists are loth to regard the adrenal cortex as epithelial. However, cells of the adrenal cortex and its tumours are epithelium like in their general structure and arrangement, and most pathologists think of them as epithelial. Hence I can see little real objection to applying the name *carcinoma* to the tumours. Again, no sharp separation of benign and malignant growths is possible, whether a large circumscribed but growing tumour shall be regarded as an unusually active *adenoma* or as a *carcinoma* which has not yet displayed invasiveness or metastasis is a matter of personal preference.

Bulloch and Sequera's paper in 1905 was the first in this country to concentrate attention on the association of adrenal cortical tumours and sexual development. In 1912 Glynn published his classical account of the subject which he amplified in 1921 in a further important paper. Proof of the endocrine activity of the tumours was afforded by improvement in the signs of virilism following surgical removal of the tumours as in the cases described by Holmes (1925) and Murray and Simpson (1927). More recent reviews and general accounts of the subject include those of Kepler, Kepler and Keating, Simpson and Joll, Broster *et al* and Cahill *et al*.

(1) Age and sex incidence

No age is exempt the tumours have been found in infancy and in old age but most patients have been between 25 and 45 years of age. Females are affected much more often than males and the same sex difference is seen in pre adolescents as in adults. In 1939 Reilly *et al* found records of 40 cases in pre adolescent girls, while in 1941 Kepler and Keating could find only 17 cases in boys.

(d) Other endocrine changes

Adrenal cortical tumours may produce any of the symptoms comprised in Cushing's syndrome of so called "pituitary basophilism" (Lescher and Robb Smith, Hare *et al*, Kepler and Keating, Cahill *et al*) These symptoms include purplish cutaneous striae, raised blood pressure and patchy decalcification of the skeleton, as well as hirsutism and obesity. These changes point to the close interrelationship between the pituitary and adrenal glands, discussed fully by Vines and by Burrows, and they also show that "pituitary basophilism" is not a proper synonym for Cushing's syndrome, a question already discussed in Chapter 38.

Hormonal assays of the urine of patients with virilism or feminism due to adrenal cortical tumours have substantiated that these effects are due to excessive production of androgens or oestrogens respectively. Patterson *et al*, Anderson *et al*, Callow and Crooke, and other workers cited by Burrows have demonstrated excess of androgenic steroids in the urine of patients with virilism. Burrows *et al* demonstrated excessive oestrogenic hormone in the urine of the feminized male patient described by Simpson and Joll, this excess disappeared after operative removal of the tumour and returned with its recurrence (See also the discussion following Broster's paper, 1946).

Cytological studies show a relationship between the cellular structure of the tumours and their hormonal activity. The fuchsinophil reaction of Vines is strongest in tumours with androgenic properties. According to Goormaghtigh, the cells of virilizing tumours form siderophil and fuchsinophil granules, those of feminizing tumours do not, but show yellow pigment granules and those of tumours devoid of endocrine effects show neither. Ross carefully compared the structure of Simpson and Joll's specimen of feminizing tumour with that of a tumour from a woman with virilism, and found significant differences of cytology and staining properties.

Adrenal cortical dysfunction without tumour must be mentioned. Endocrine disturbances similar to those accompanying tumours can also be brought about by simple hyperplasias or even hyperfunction without enlargement of the glands. In many cases of this kind recorded by Broster *et al*, Vines found "essential hyperfunction with virilism" to be almost constantly associated with strongly positive fuchsinophil properties of the adrenal cortex, while in cases of Cushing's syndrome the fuchsinophil test was usually negative or only weakly positive.

ADRENAL CORTICAL TUMOURS IN ANIMALS

Adenomas or carcinomas of the adrenal cortex are amongst the commonest visceral tumours of cattle, Feldman (1932) saw 19 examples and referred to others and Rudduck and I studied 4 specimens. Although these tumours are often large, vascular and necrotic most of them are well circumscribed and devoid of metastases. In sheep also, adrenal cortical tumours are one of the commonest forms of new growth. Feldman (1931) saw 10 cases, with unilateral tumours in 7, bilateral tumours in 3 animals, although these appeared histologically malignant no metastases were present. Rudduck and I examined bilateral cortical adenomas from 2 dogs. Feldman refers to one recorded instance of adrenal carcinoma in a horse. Curtis *et al*, Ratcliffe Hueper and Ichniowski,

(3) Endocrine results of adrenal cortical tumours

The complexity of this subject can be gauged from a perusal of Part VI of Burrows's book on the sex hormones. From the normal adrenal cortex, more than a score of different but related sterol substances have been isolated, some of them androgenic, some oestrogenic some with progestin effects, and some with more general metabolic effects not related to sexual characters. It is then not surprising that adrenal cortical tumours should produce a wide range of endocrine disturbances and that analysis of the syndromes produced should still be far from complete.

However the main syndromes originally outlined by Glynn are now fairly well understood in terms of the properties of androgenic, oestrogenic and other substances known to be elaborated by the cortex and its tumours. These syndromes varying with the particular hormones secreted and with the age and sex of the patient can be conveniently grouped thus

(a) *Tumours with no recognizable hormonal results*

Examples and references are given by Kepler and Keating and by Cahill *et al*. Some of these growths have been highly malignant anaplastic ones but others have shown well differentiated tissues.

(b) *Tumours with changes due to excess of androgens*

These form by far the largest group which is divisible into four sub groups according to age and sex

- (i) *In female infants or children* the usual results are precocious growth and sexual development of male type with enlarged clitoris and labia and sometimes if the tumour occurs in foetal life atresia or other malformations of the vagina. The child may thus have pseudo hermaphrodite characters and there may have been doubt as to its true sex. Adiposity may also occur. Reilly *et al* reviewed 40 cases in pre adolescent girls.
- (ii) *In female adults* there occur voice changes hairiness of male distribution coarsening of skin acne amenorrhoea adiposity the development of masculine contours and atrophy of breasts and internal genitalia.
- (iii) *In male children* premature sexual skeletal and muscular development are observed.
- (iv) *In male adults* as might be expected, endocrine results are often not apparent.

(c) *Tumours with changes due to excess of oestrogens*

The most striking instances are in adult males the symptoms include impotence atrophy of the genitalia and mammary enlargement and secretion (Mathias Busch Burrows *et al* Simpson and Joll). Oestrogen secreting tumours in adult females probably produce no special endocrine result but occurring in young children they may cause premature feminine puberty and menstruation as in Bulloch and Sequiera's case.

CHAPTER 40

TUMOURS OF THE PARATHYROID GLANDS

INTRODUCTION

WHEN in 1891 von Recklinghausen gave his classical description of generalized fibrocystic disease of bone, the parathyroid origin of this disease was unsuspected. The story of the discovery of this relationship, foreshadowed in 1904 by Askanazy's observation of a case of associated parathyroid tumour and von Recklinghausen's disease, and culminating in Mandl's successful treatment of such a case by parathyroidectomy in 1926, is well told by Drennan, Barr and Bulger, Hunter and Turnbull, Elmslie *et al*, Castleman and Mallory and Alexander *et al*, to whom the reader is referred for fuller details and examples. Before 1926, the relationship of parathyroid dysfunction and osteitis fibrosa had still been debatable. Many workers had observed enlargement of the parathyroids as a secondary result of various skeletal diseases, and as late as 1923, Dawson and Struthers, in their excellent account of a typical case of associated generalized osteitis fibrosa and parathyroid tumour, concluded that the latter was a sequel of the former. However, the therapeutic effect of parathyroidectomy made it clear that generalized fibrocystic disease of bone was the result of hyperparathyroidism.

Most parathyroid tumours have been classified as benign adenomas and relatively few of them as carcinomas, but, although this subdivision is useful and justifiable, there is no sharp separation of the two groups. Castleman and Mallory also sharply distinguished between cases showing generalized hyperplasia affecting all parathyroid bodies simultaneously and true neoplasms arising focally in one, or occasionally two, glands and growing progressively. However, while hyperparathyroidism sometimes results from non-neoplastic hyperplasia or hyperfunction, in most cases it is due to true tumour formation. Thus Castleman and Mallory, in their analysis of 160 previously recorded cases of hyperparathyroidism and 25 cases of their own, found that tumours outnumbered cases of simple hyperplasia sevenfold. We are concerned here with the true tumours only but it must be admitted I think, that multiple tumour formation may sometimes be difficult to distinguish from hyperplasia.

My own experience of parathyroid tumours is limited to the following two cases, one with and the other without signs of hyperparathyroidism.

Case I (Dr J Le M. Kneebone's case).—History.—A man 67 years of age with advanced generalized fibrocystic disease of bone and with hypercalcaemia and hypophosphataemia was operated on and a left-sided parathyroid tumour which extended down into the mediastinum was removed. This weighed 60 grammes and consisted of uniform greyish brown firm tissue. A palpable tumour 2 centimetres in diameter in the right side of the neck was not removed. After the operation the blood-calcium and phosphate values became normal and treatment was directed to mechanical straightening of the deformed femora. *Histology.*—The tumour is a typical parathyroid adenoma consisting mainly of clear principal cells arranged in cords and folded masses with small spaces and pseudo-acinar structures in places (Figs 314 and 315).

and Heiman observed adrenal cortical tumours in rats Berner (cited by Holmes) is said to have seen virilism in a hen with an adrenal tumour

REFERENCES

- Anderson A F Ham A M and Patterson J (1943) *J Path Bact* 55 341
 Broster L R and Vines H W C (1935) *The Adrenal Cortex* London
 Broster L R Vines H W C Patterson J Greenwood J G Allen C Marnan G F and Butler G C (1938) *The Adrenal Cortex and Intersexuality* London
 Broster L R (1939) *Brit J Surg* 26 925
 Broster L R (1946) *Proc Roy Soc Med* 40 35
 BULLOCH, W and SEQUIERA J H (1905) On the relation of the suprarenal capsules to the sexual organs *Trans Path Soc Lond* 56 189 (A classical and excellent paper)
 Burrows H Cook J W Roe E M F and Warren F L (1937) *Biochem J* 31 950
 BURROWS, H (1945) *Biological Actions of Sex Hormones* Cambridge
 Busch J P (1927) *Dtsch med Wschr* 53 323
 CAHILL G F, MELICOW, M M and DARBY H H (1942) Adrenal cortical tumors *Surg Gyn Obst* 74 281 (A good general account)
 Callow N H and Crooke A A (1944) *Lancet* i 464
 Curtis M R Bullock F D and Dunning W F (1931) *Amer J Cancer* 15 67
 Feinblatt H M (1926) *Arch Int Med* 38 469
 Feldman W H (1931) *Amer J Cancer* 15 2044
 Feldman W H (1932) *Neoplasms of Domesticated Animals* Philadelphia
 GLYNN E E (1912) The adrenal cortex its rests and tumours its relation to other ductless glands and especially to sex *Quart J Med* 5 157
 GLYNN, E E (1921) A comparison between ovarian hypernephroma and luteoma and suprarenal hypernephroma with comments on suprarenal virilism' *J Obst Gyn* 28 23 (Glynn's papers are unsurpassed classics)
 Goormaghtigh N (1940) *Amer J Cancer* 38 32
 Hare D C Ross J M and Crooke A C (1935) *Lancet* ii 118
 Heiman J (1944) *Cancer Res* 4 430
 Holmes G (1925) *Quart J Med* 18 143
 Hueper W C and Ichniowski C T (1944) *Cancer Res* 4 176
 KEPLER F J (1935) Diseases of the adrenal glands *Arch Int Med* 56 105
 KEPLER F J and KEATING F R (1941) Diseases of the adrenal glands *Arch Int Med* 68 1010 (Valuable reviews)
 Lescher F G and Robb Smith A H T (1935) *Quart J Med* 4 23
 Mathias E (1922) *Virchows Arch* 236 446
 Murray C G and Simpson G S (1927 and 1929) *Lancet* 1927 ii 745 1929 i 466
 Patterson J McPhee I M and Greenwood A W (1942) *Brit Med J* i 35
 Ratchiffe H L (1940) *Amer J Path* 16 237
 Reilly W A Lissner H and Hinman F (1939) *Endocrinology* 24 91
 SIMPSON S L and JOIL C A (1938) Feminization in a male adult with carcinoma of the adrenal cortex *Endocrinology* 22 595 (A good account and discussion)
 VINES H W C (1938) The adreno-genital syndrome some histological observations In *The Adrenal Cortex and Intersexuality* by Broster et al (qv) p 135
 Willis R A (1934) *The Spread of Tumours in the Human Body* p 277 London

cerebello-pontine angle adherent to the dura above the foramen magnum and microscopically a typical meningioma and (c) multiple cortical adenomas of both adrenal glands (The multiplicity of tumours in this case is noteworthy)

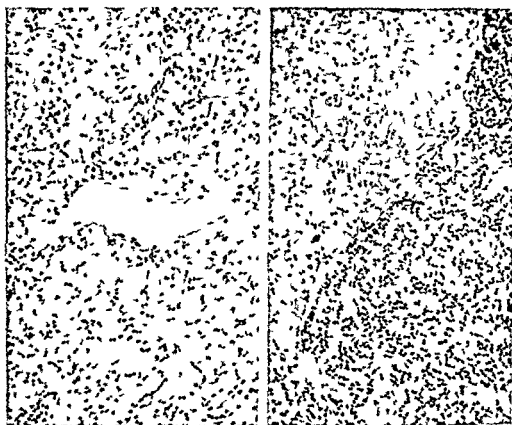


FIG 316—Case II Parathyroid adenoma showing distinct cell types ($\times 120$)

INCIDENCE AND CAUSATION

(1) Age

Castleman and Mallory found the following age distribution of 154 cases of functioning adenoma

Decades - - -	1	2	3	4	5	6	7	8	9	Total
Number of cases -	0	10	25	27	37	38	11	5	1	154

(2) Multiplicity

The tumours are usually single. Hunter and Turnbull's review comprised 24 cases with solitary tumours and 3 cases with two tumours each.

(3) Sex

In all recorded series females outnumber males, usually in the ratio of about 2 to 1, e.g. 108 women to 45 men in Castleman and Mallory's analysis, 10 to 4 in Alexander's cases.

Case II—History—An obese woman of 55 years who had had irregular metrorrhagia for 12 years underwent hysterectomy for multiple large uterine myomias and became

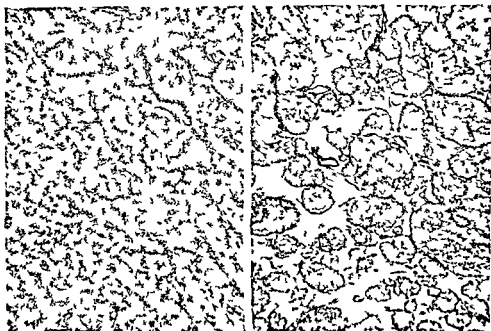


FIG 314—*Case I* Parathyroid adenoma clear-celled trabecular and pseudo acinar structure ($\times 64$)

comatose and died the day following the operation. *Necropsy* disclosed (a) a yellowish ovoid tumour 2.5×1.5 centimetres in the position of one of the inferior parathyroids microscopically a parathyroid adenoma composed mainly of large solid liver like oxyphil

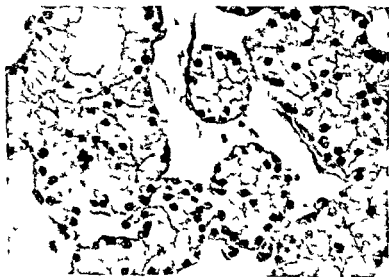


FIG 315—*Case I* Details of Fig 314 ($\times 320$)

cells but with also areas of small cuboidal cells in acinus like clusters and of vacuolated clear cells (Fig 316) (b) a well-defined tumour 4 centimetres in diameter in the right

described by Gentile *et al*, excision of the primary tumour resulted in the return of the blood chemistry to normal, the later development of a metastatic deposit in a lymph gland was accompanied by return of the chemical changes of hyperparathyroidism, which again disappeared after removal of the metastasis, and the patient remained free of further recurrence 4 years from the time of the original operation. This case was also notable in showing microscopic invasion of small veins by the growth. The cases of Alexander *et al* were diagnosed as "carcinomas" because of their cytology and capsular invasion, but they produced no metastases and did not recur after removal.

THE RESULTS OF HYPERPARATHYROIDISM

Details of the now well known alterations of bone structure and blood chemistry brought about by hyperfunctioning parathyroid tumours will be found in the papers already cited, and need be summarized only briefly here.

(1) The bones

The classical features of von Recklinghausen's disease are beautifully depicted in the papers of Dawson and Struthers and of Hunter and Turnbull. The principal changes are decalcification, fibrous replacement, cyst formation, osteoclastomas, and fractures and deformities. The "osteoclastomas", consisting of giant celled tissue closely resembling that of the giant cell myelomas, occur in more than 50 per cent of cases, since they disappear after removal of the offending parathyroid tumour, they are not genuine neoplasms. As Dawson and Struthers pointed out, the giant celled tissue of fibrocystic disease is a reactionary tissue related to bone resorption, and it later undergoes fibrosis and cyst formation. It is important for clinicians to know that the bone changes in hyperparathyroidism can be mistaken radiographically for Paget's disease (Couch and Robertson) and also that great enlargement of the jaw may simulate leontiasis (Cohen and Kelly).

(2) The blood chemistry

The changes include rise of serum calcium and of phosphatase and fall of serum-phosphates. These revert to normal levels following removal of the offending parathyroid tumours.

(3) Urine changes

Urinary excretion of calcium and phosphates is increased. Precipitation of these leads to intra tubular calcification of the kidney and to stone formation in the pelvis (Albright *et al*). Renal lithiasis occurs in more than half the cases with hyperfunctioning tumours, and is sometimes the cause of the first symptoms. In some cases nephrectomy or other surgical treatment for calculi has been carried out years before recognition of their cause, as in Cohen and Kelly's case.

(4) Metastatic calcification

This may take place in many organs besides the kidneys e.g. in the gastric mucosa and alveolar walls of the lungs in Barr and Bulger's third case and in almost every tissue of the body in the case of Dawson and Struthers.

(4) Causation

Nothing is known of this. There is no evidence that simple hyperplasia of the parathyroids, whether primary or secondary to disturbances of calcium metabolism in various renal or skeletal diseases, predisposes to tumour formation. Hadfield and Rogers saw a parathyroid tumour of 64 grammes unaccompanied by hyperparathyroidism in a patient with acromegaly, and they found 6 previous reports of parathyroid adenoma or enlargement accompanying pituitary disease. Perlman also refers to the evidence suggesting a pituitary parathyroid relationship in calcium metabolism, and describes a dog in which he found pituitary adenoma, adenomatous hyperplasia of the parathyroids, skeletal decalcification and chronic nephritis. I have found no other records of parathyroid tumours in animals.

STRUCTURE AND GROWTH

Parathyroid tumours are well circumscribed and many of them encapsulated. The tissue is uniform in texture and usually brown or greyish in colour. The size attained varies, tumours of between 100 and 200 grammes have been recorded.

Most of the tumours have a microscopical structure closely like that of normal parathyroid tissue, consisting of trabeculae of characteristic clear cells or less often of oxyphil cells or of both. Study of the tumours confirms the opinion of most histologists that there is no essential difference between these two varieties of cells but that they are the same cells seen in different phases of activity, all combinations and transitions of the two varieties are seen in the tumours. Tumours consisting mainly or wholly of clear cells show a close resemblance microscopically to clear celled renal carcinoma especially when the presence of cystic spaces and convolution of the trabeculae give the growth a pseudo glandular pattern (see Figs 314-315). The structure is usually well differentiated and uniform throughout, only a minority of tumours showing irregularities of cellular structure and arrangement. Alexander *et al* depict cellular and nuclear pleomorphism, giant tumour cells, mitotic figures and invasion of the tumour capsule.

MALIGNANT PARATHYROID TUMOURS

In a small minority of cases, invasive properties or very rarely metastases denote some degree of malignancy. Guy, Gentile *et al* and Alexander *et al* have reviewed the records of such cases. In some of these the details given are scanty and doubt remains regarding the identity of the tumours. Reports of malignant tumours of this region supposed to be of parathyroid origin but without evidence of hyperparathyroidism must be examined very critically, and it must be remembered particularly that a parathyroid origin has been attributed erroneously to some thyroid tumours (qv). However, in some reported cases the signs of hyperparathyroidism have been present or the structure has been characteristic. Malignancy of such cases has been restricted to local invasion of slight or moderate extent or local lymph nodal metastases. I know of no fully substantiated instances of metastasis of parathyroid tumours by the blood stream. In Guy's case local recurrences invaded the skin. In the case

CHAPTER 41

INTRODUCTION TO MESENCHYMAL TUMOURS, FIBROBLASTIC TUMOURS AND MYXOMAS

INTRODUCTORY REMARKS ON THE MESENCHYMAL TISSUES AND THEIR TUMOURS

(1) Intermutability of mesenchymal tissues

IN THE past, students of normal histology have been too apt to assume that the different kinds of tissues and cells in the adult are permanently determined invariable structures, each a distinct immutable species capable of producing by proliferation cells of its own kind only. A study of pathological histology, i.e. of what the various cells can be and do in all manner of abnormal environments, soon corrects this error and shows that great transformations of cellular structure—metaplasias—are possible in most tissues. The cells have much wider potencies for differentiation than are ever displayed in health, abnormal conditions of growth are needed to reveal their dormant potencies or plasticity.

In no other group of tissues are metaplasias as frequent or as important for the pathologist as in the derivatives of the mesenchyme—fibrous, mucoid, adipose, synovial, meningeal, cartilaginous, osseous, haemopoietic, vascular and reticulo-endothelial tissues. As a striking instance of the protean potencies of reparative mesenchymal tissue may be mentioned the metaplastic formation of bone and bone marrow in scars or old inflammatory foci or in the walls of arteries. Not only is the bone formed *in situ*, but so also are all the elements of the marrow—haemopoietic cells, megakaryocytes, reticular elements and fat cells, cartilage also is often present along with the bone. None of these can be immigrants, they must all arise by divergent differentiation from the local fibroblastic and vasoformative elements of the reparative tissue. Conversely bone is reconvertible into connective tissue. 'osteitis fibrosa', Paget's disease and many other decalcifying and fibrous replacement lesions exemplify the fibrous metaplasia of osseous tissue. Clearly then, the fibroblast, lipoblast, osteoblast, angioblast etc. are not as has often been assumed sharply separate species for under pathological circumstances, proliferating cells of these kinds may redifferentiate into cells of other kinds. Proliferating mesenchymal tissue, typified by reparative granulation tissue with its fibroblasts and blood vessels, can produce all or nearly all that embryonic mesenchyme can produce. In brief, regeneration is resumed embryonic growth and metaplasias are the evidence of resumed embryonic plasticity. The multiplying cells of a regenerating mesenchymal tissue "undergo a true rejuvenescence, and approach once more an embryonic condition. The cells become less differentiated *de facto* as well as in appearance. This can only mean that some of the earlier potencies are reacquired" (Nicholson 1923).

Finally it is to be noted that not all parathyroid tumours produce hyperparathyroidism, occasionally clinical examination or necropsy reveals a tumour which has occasioned no demonstrable hormonal results (Hadfield and Rogers and my Case II)

REFERENCES

- Albright F Baird P C Cope O and Bloomberg E (1934) *Amer J Med Sci* 187 49
 Alexander H B Pemberton J de J Kepler E J and Broders A C (1944) *Amer J Surg* 65 157
 Barr D P and Bulger H A (1930) *Amer J Med Sci* 179 449
 CASTLEMAN, B and MALLORY T B (1935) The pathology of the parathyroid gland in hyperparathyroidism A study of 25 cases *Amer J Path* 11 1 (A valuable review)
 Cohen H and Kelly R E (1933) *Brit J Surg* 20 472
 Couch J H and Robertson H F (1941) *Surg Gyn Obst* 73 165
 DAWSON J W and STRUTHERS J W (1923) Generalized osteitis fibrosa with parathyroid tumour and metastatic calcification including a critical discussion of the pathological processes underlying osseous dystrophies *Edinb Med J* 30 421 (A detailed study of the skeletal changes)
 Drennan A M (1930) *J Path Bact* 33 65
 ELMSLIE R C FRASER F R DUNHILL T P VICK R M HARRIS C F and DAUPHINEE J A (1933) The diagnosis and treatment of generalized osteitis fibrosa with hyperparathyroidism *Brit J Surg* 20 479
 Gentile R J Skinner H L and Ashburn L L (1941) *Surgery* 10 793
 Guy C C (1929) *Surg Gyn Obst* 48 557
 Hadfield G and Rogers H (1932) *J Path Bact* 35 259
 HUNTER D and TURNBULL, H M (1931) Hyperparathyroidism generalized osteitis fibrosa with observations upon the bones the parathyroid tumours and normal parathyroid glands *Brit J Surg* 19 203 (A valuable review and a beautifully illustrated study of 4 cases)
 Mandl F (1926) *Arch klin Chir* 143 1
 Perlman R M (1944) *Arch Path* 38 20

Appreciation of the variability of the mesenchymal tissues will save the pathologist from accepting over-rigid conceptions of classification, from inventing artificial sub divisions within the main tumour types and from participating in pointless discussions over the histogenesis of tumours exhibiting aberrant differentiation

(3) "Benign" and "malignant", relative terms

The main thesis of Chapter 3, that "innocence" and "malignancy" are not distinct properties of tumours but are merely terms of prognostic convenience, is particularly pertinent to mesenchymal tumours. Between fibromas and fibrosarcomas, lipomas and liposarcomas, chondromas and chondrosarcomas, lymphomas and lymphosarcomas, no sharp lines of demarcation can be drawn. Each tumour must be judged on its own merits—on its rate of growth, its cellular structure, and its powers of infiltration or metastasis. Many a 'fibroma' or 'chondroma', adjudged benign from its microscopic structure and slow rate of growth, has yet recurred or metastasized. On the other hand, many a cellular fibroma, the microscopic structure of which has justifiably caused anxiety, has yet been well circumscribed and has been cured by simple enucleation. Some 'benign' giant cell tumours of bone have metastasized and proved fatal. While there are, of course, a great many mesenchymal tumours the malignancy of which is plain from their microscopic structure, there are also many others for the prognosis of which great histopathological experience is necessary—and even then mistakes will be made. In the following chapters benign and malignant tumours of each cell type are considered together—fibroma and fibrosarcoma, chondroma and chondrosarcoma, and so on.

(4) The meaning of "sarcoma"

A sarcoma is a malignant tumour arising from any non epithelial mesodermal tissue—fibrous, mucoid, fatty, osseous, cartilaginous, synovial, lymphoid, haemopoietic, vascular, muscular or meningeal. The simplest nomenclature specifies each form of sarcoma by an appropriate prefix: fibro, myxo, lipo, osteo, etc. It has not been customary to think of the leukaemias, Hodgkin's disease and plasma cell tumours as "sarcomas", or to speak of malignant meningeal or synovial tumours as 'meningiosarcoma' or "synoviosarcoma", but it is quite justifiable to do so, for these are all malignant non epithelial mesenchymal neoplasms. Malignant tumours of serosal and vascular endothelium, if such indeed occur, would also be embraced by the definition. The inclusion of all these diverse forms of growth under the one generic name 'sarcoma' is warranted not only by the common mesenchymal origin of their parent tissues, but also by their general similarity of behaviour. The definition properly excludes two special forms of malignant non epithelial tumour, glioma and chordoma, both of non mesenchymal origin.

Every kind of tumour is recognized histologically by its cellular differentiation. An epithelial tumour can only be recognized as such if its cells show some degree of epithelial aggregation; if, as often happens, a carcinoma is so anaplastic that its cells have lost all polarity and arrangement, then the microscopist cannot affirm its epithelial nature. So also, the microscopist alone can affirm the sarcomatous nature of a tumour only when it displays a recognizable degree of

Histologists describe the presence in the connective tissues of the adult body of undifferentiated mesenchymal cells. These presumably have the potencies of embryonic mesenchymal cells and may be supposed capable of differentiating into any of the adult tissues derived from mesenchyme. It is quite probable that these cells may be the source of some of the mesenchymal tumours. But it would be splitting hairs to debate whether or not these cells or the differentiated cells of the tissues are the usual origin of tumours. For most kinds of adult cells of mesenchymal origin can multiply and when they do so they often display their reacquisition of embryonic potencies by redifferentiating in aberrant directions. The young multiplying progeny of formerly differentiated cells probably possess pluripotency equivalent to that of undifferentiated mesenchymal cells which have never matured.

(2) The kinship of the various mesenchymal tumours

The plasticity or capacity for diverse differentiation plainly seen in simple regenerative proliferations of the mesenchymal tissues is amply evident also in their tumours and has led to many needless disputes over histogenesis and classification and to complicated and redundant terminology. Names like *fibro-angio-myxoma* or *haemangio-elasto-myxoma* or *chondro-myxo-haem-angio-endothelio-sarcoma* (names which have actually been used) while they may be tolerable as shorthand descriptions are all too apt to be invested with histogenetic implications and so to impede clear thought. The very use of such names shows plainly the plasticity of the proliferating tissues, a plasticity which makes a rigid classification of mesenchymal tumours impracticable. *Fibromas* *chondrify* or *ossify*. *Osteogenic sarcomas* contain cartilaginous or fibrous areas, *fibromas* contain *myxomatous* areas and vice versa. *Lipomas* are often partly or predominantly *fibromatous*. The *fibromatous* component of *mammary fibroadenomas* becomes *cartilaginous* or *bony*. *Predominantly vasoformative* (*angiomatous*) areas are found in tumours of other kinds. All gradations and combinations are seen between the several named variants of *lymphoid tumours*—*lymphatic leukaemia*, *lymphosarcoma*, *Hodgkin's disease* and *reticulosarcoma*, and endless confusion has resulted from attempts to segregate a group of *endotheliomas* from other mesenchymal growths. Of great interest is a report by Gilmour of a recurrent tumour in an adult which consisted of mucinous tissue like embryonic mesenchyme with also *lipoblasts* and *haemopoietic cells* and for which therefore the suggested name '*mesenchymoma*' is appropriate.

Of course just as it is necessary and useful to distinguish by appropriate names the various differentiated normal tissues derived from mesenchyme so also it is necessary and useful to distinguish by corresponding names the various tumours showing predominant differentiation of this or that type. It is also true that the kind of differentiation exhibited by a tumour is in most cases wholly or mainly that of the tissue from which it has sprung e.g. that *osteogenic tumours* usually spring from bone, *cartilaginous tumours* from cartilage, *fibroblastic tumours* from connective tissue and so on. The cell types of the several differentiated kinds of mesenchymal tissue naturally tend to be perpetuated in their tumours. But it is a mistake to be misled by terminology into assuming that the species either of the normal tissues or of their neoplasms are unrelated and immutable.

that cell will cease to be "endothelial". So also synovial "endothelium" consists merely of mesenchymal cells which have come to line a synovial cavity. No sharp distinction can be made between these cells and the subjacent fibroblasts of the synovial membrane. Synovial "endothelium" and synovial fluid can develop from non synovial connective tissue when mechanical conditions are appropriate, as in false joints and bursae. The special properties of endothelial cells of all kinds are, in fact, properties acquired by mesenchymal cells placed in certain positions with respect to special body fluids or other environmental factors.

(ii) *Do characteristic tumours arise from endothelium?* Tumours do, of course, arise from and tend to reproduce the specific structures of, vascular, synovial or meningeal tissues. But these already have their appropriate names and nothing is gained by embracing them under the further common label 'endothelioma', an angioma, a synovioma and a meningioma have no more in common than other tumours of mesenchymal origin. To force them together under a common name merely because they all represent tissues which have flat celled surfaces is artificial and an affront to histogenetic principles. It is necessary to add here that most so called 'angiomas' are not even tumours, but malformations, so that their artificial alliance with true tumours like meningiomas is particularly confusing.

If it be argued that the name "endothelioma" (or "mesothelioma") is still useful to designate a distinctive group of malignant tumours with vasoformative, reticulo endothelial or coelom formative characters, I reply (a) that for the very rare malignant angiomas the name "angiosarcoma" is preferable, as being uniform with the names of other specific kinds of sarcoma and as being less cumbersome than "haemangio endothelioma", (b) that for the rare spindle celled or pleomorphic celled primary tumours of lymphoid tissue "reticulo sarcoma" is the appropriate specific name, (c) that I have not seen an acceptable report of a primary coelomic "endothelioma", and that the only tumour which I myself ever ventured to diagnose as such, a tumour in a hydrocele, turned out to be a metastasis from an undetected bronchial carcinoma (Willis, 1938), and (d) that the great majority of reports of supposed 'endotheliomas' whether of lymph glands, serous cavities or bones are either wholly inadequate or carry clear internal evidence that the tumours were secondary to undiscovered primary growths elsewhere (see Chapter 10).

Further, there are no histogenetic grounds for supposing that a sarcoma arising from the layer of cells lining a vascular or coelomic space would be any different from a sarcoma arising from the immediately extravascular or subserous cells. As we have seen the surface cells are what they are by virtue of their positions. If in a tumour they cease to hold surface positions they will cease to be "endothelial" cells. Confronted then by a cellular vascular sarcoma, how shall we decide whether on the one hand it arose exclusively from preformed vascular endothelium and that its vessels display its vasoformative properties or on the other hand from indifferent fibroblastic or other mesenchymal tissue and that its vessels represent merely the inevitable blood supply of a growing cellular tissue? The problem is the same as that of the origin and potencies of the vascular and extravascular cells in reparative tissue, and the solution is the same namely, that all these young mesenchymal cells are plastic and interconvertible, and disputation over their 'endothelial' or 'non endothelial' nature is pointless.

differentiation towards one or another of the non epithelial mesodermal tissues i.e. if it is recognizable as a fibrosarcoma an osteosarcoma a leiomyosarcoma etc. A completely anaplastic sarcoma is indistinguishable by microscopic study alone from any other completely anaplastic growths. These considerations though self evident are constantly being ignored in medical and pathological literature. Neoplasms are dubbed sarcomas (round celled, spindle celled, mixed celled or giant celled) merely because parts of them often only small biopsy fragments, have been found diffusely cellular. Some writers go even further in their preconceptions of sarcomatous structure and seeing epithelial clumping amidst diffuse tumour tissue call tumours alveolar sarcoma carcino sarcoma or 'sarcoma carcinomatoides'. These sources of confusion have already been discussed in Chapter 8 (and see Willis 1932). Here I repeat my conviction that excluding tumours sufficiently differentiated for positive histological identification there is no type of structure alleged to be characteristic of any form of sarcoma (or endothelioma) which may not be perfectly imitated by areas of atypical carcinoma.

This warning against the all too prevalent mistake of calling tumours 'sarcomas' just because they are anaplastic and diffusely cellular does not of course imply denial of the existence of anaplastic cellular sarcomas. But the recognition of such tumours as sarcomas depends upon evidence other than the microscopic namely on the knowledge that the primary growth arose in some non-epithelial organ such as a lymph gland a bone or a muscle and this knowledge is often not certain unless complete necropsy has shown that the presumed primary growth was indeed primary and not a metastasis from some unsuspected tumour elsewhere. Histological diagnosis must not be allowed to run ahead of the available evidence and when the evidence is still inconclusive the wise pathologist will be content to diagnose undifferentiated cellular malignant neoplasm of uncertain origin.

(5) Endothelioma

This is the place to record once and for all my opinion of this much abused name. Two questions must be answered—(i) What is endothelium? and (ii) Do any specifically characteristic tumours arise from it?

(i) *What is endothelium?* Most would agree that this name is usefully applied to the flat layers of cells lining vascular and serous cavities to which some would add the layers of cells lining meningeal and synovial cavities. Now both embryology and pathology show plainly that these flat layers of cells are endothelial not by virtue of any specific properties of the cells but by virtue of their positions. Studies of the proliferation and fate of fibroblasts and vasoformative cells in reparative tissue show that vascular channels in this tissue appear and disappear repeatedly in accordance with purely mechanical factors. This plasticity of all the elements in young mesenchymal tissue should cause no surprise to the pathologist and surgeon both of whom know well that the highly vascular granulation tissue of today rich in endothelial channels will in a few weeks be an avascular scar devoid of endothelium and containing only fibrocytes. The young multiplying cells in the reparative tissue are ready to become either endothelial cells or fibrocytes (yes or osteocytes or chondrocytes or fat cells or haemopoietic cells) as may be determined by local conditions. An endothelial cell is merely one which has come to line a vascular channel and when that channel disappears

Between cellular anaplastic highly malignant growths of this kind and slowly growing, densely fibrous, benign growths structurally resembling normal fibrous tissue, there is a complete series of tumours of intermediate structure and behaviour



FIG 317—An area of early chondrification in a partly cartilaginous subcutaneous fibroma 3 centimetres in diameter from a woman aged 27 ($\times 120$)

Moreover, primarily fibrifying tumours cannot be sharply separated from other mesenchymal growths, for some of them show metaplastic mucinous change, chondrification or ossification (Fig 317), or admixture with adipose cells. It is merely a matter of personal preference whether to apply to these tumours such names as 'chondro fibroma' and "myxo fibrosarcoma" or to call them "chondrifying fibroma" and "fibrosarcoma with mucinous change".

I do not intend to repeat the well known descriptions of the structure of fibromas and fibrosarcomas—their varying degrees of cellularity and of collagen content, the latter determining their texture and their hardness or softness. All gradations and combinations between dense tendon like fibrous tissue and undifferentiated pleomorphic celled sarcoma are encountered. The latter shows great cellular variety, often including many giant and multinucleated tumour cells, the fibroblastic nature of these, and also of poorly collagenous spindle celled fibrosarcomas is often uncertain for it is difficult to distinguish included collagen fibres from fibres formed by the tumour cells.

(2) General behaviour

While highly differentiated, densely fibrous tumours usually behave as benign fibromas there are exceptions to this rule as in the following two examples

*Case I (reported in detail in 1938)—History—*A man aged 49 had noticed a swelling of his tibia for a year. Skiagrams showed an expanding central radio translucent lesion thought to be either osteitis fibrosa or a benign tumour. Excision of the middle third of the tibia with insertion of a bone graft was performed. The lesion showed dense

Briefly then, my position is that for well differentiated growths of those mesenchymal tissues which happen to possess surfaces we already have adequate distinctive names and that for poorly differentiated sarcomatous growths of these tissues the name endothelioma is still unnecessary and in view of what we know of the plasticity of multiplying mesenchymal cells, inappropriate

(6) The ubiquity of mesenchymal tissues and regional peculiarities of their tumours

Mesenchymal tissues are ubiquitous so that no part of the body is exempt from mesenchymal tumours. This widespread distribution of tumours of any given type makes a general analysis of their properties not only difficult but also of doubtful value for differences of site are accompanied by differences of behaviour. Thus fibromas of nerve sheaths, fibromas of bones and fibromas of the abdominal wall though all consisting of broadly similar fibroblastic tissue show many differences of age and sex incidence, structure and behaviour. Strictly speaking then the only satisfactory way of discussing the characters of tumours of a given cell type is to do so piecemeal, region by region. This however would entail a great deal of repetition regarding those general features of structure and behaviour which are common to the whole class. In the following chapters I have attempted to strike a compromise between a broad survey of each class and particular accounts of those regional subclasses with peculiar features. In doing this I have deliberately omitted or curtailed descriptions of those characters of the various tumours which are well known and adequately presented in most text books and have preferred to draw attention to less familiar features and viewpoints.

(7) Frequency and causation of mesenchymal tumours

Considering the abundance and ubiquity of mesenchymal tissues in the body, and their ready proliferative response to injury, mesenchymal tumours are surprisingly infrequent. This fact alone is significant as regards the supposed traumatic and irritational causation of tumours, although reparative and chronic inflammatory changes are everyday occurrences, mesenchymal neoplasia is rare. Experimental results confirm this: fibroblastic and other sarcomas though readily evoked by specific carcinogenic agents are rarely if ever produced by non specific injuries (see Chapter 4). The mesenchymal tumours produced experimentally by carcinogenic agents resemble in structure and behaviour those occurring spontaneously in animals and man. It therefore seems reasonable to assume that the spontaneous growths are likely to be due to similar specific agents and to search for these in the histories and environments of the patients. At least one kind of mesenchymal tumour in man, the osteosarcoma of workers in radio active materials, is already known to be caused by an external agent, another leukaemia in benzol workers is strongly suspected, and further instances will no doubt be brought to light by future research.

PREDOMINANTLY COLLAGENOUS TUMOURS: FIBROMA AND FIBROSARCOMA

(1) General structure

Mesenchymal tumours the cells of which recognizably differentiate as collagen forming fibroblasts are fibromas or fibrosarcomas according to their behaviour

as some workers have done, that all or most fibroblastic tumours are neurogenic, there are many fibromas devoid of evidence of a relationship to nerves

(4) Dermal fibromas

(a) *Sclerosing angiomas*

The skin is, of course, an important site of neurofibromas. But in addition to these, there also occur in the dermis small well defined but non encapsulated yellowish tumours consisting of spindle shaped, irregular or multangular fibroblasts along with more or less abundant collagen and thick walled narrow blood vessels, well depicted by Harvey *et al* in their Figures 16-19. The collagen fibres are often densely aggregated into well defined sometimes hyalinized bands, continuous at the tumour margins with the fibrous bands of the dermis. These growths have been variously designated by dermatologists and pathologists as 'dermatofibroma', 'xanthofibroma', 'sclerosing angioma', 'fibrosarcoma' and 'spindle cell sarcoma' (Stecker and Robinson). They are indolent, quite benign growths, rarely attaining a diameter of more than 1 or 2 centimetres in as many years, and not suffering ulceration save accidentally. Most of those which I have studied have been from the foot or leg but I have seen them also from the hand forearm, thigh and neck. Their precise histogenesis is uncertain. The absence of encapsulation and the occasional inclusion of dermal nerves in their spreading margins do not justify the assumption that they are neurofibromas, which in other respects they do not resemble. Their plentiful content of small vessels or of structures like obliterated vessels suggests the probability that they are sclerosing angiomas. The cause of their yellow colour deserves further investigation, it is not due to foam cell accumulations, Harvey *et al* demonstrated intra cellular haemosiderin in one of their specimens.

(b) *Keloids*

Keloids form a distinct class of growths of the dermis. These densely fibrous, persistently recurrent hyperplastic scars are adequately described in most surgical works. It is doubtful whether they are true neoplasms, the local or general predisposition of the skin of those affected, the special liability of dark skinned races to keloid formation and the general characters of the lesions, all suggest rather some non neoplastic disturbance of reparative growth.

(5) Fibroma or 'desmoid tumour' of the abdominal wall

This rare growth, 66 specimens of which were reviewed by Stewart and Mouat (1924) and 77 by Pearman and Mayo (1942) is a very distinctive one. In more than 80 per cent of the cases the patients have been parous women and in most of the remainder of the cases the growths have arisen at the sites of operation scars or other injuries. The tumours develop usually during the third or fourth decades of life. They arise from the muscular aponeuroses of the abdominal wall usually below the level of the umbilicus and only rarely in the midline. They are non encapsulated, and infiltrate the neighbouring muscles which become included and atrophied in the growth. They may attain a great size. 17

fibrous tissue with cysts and was diagnosed microscopically as osteitis fibrosa. The graft failed, a sinus persisted and amputation through the upper third of the leg was performed 7 months later. The patient then remained well for a year when swelling of the amputation stump was noticed. Skiagrams showed a large soft tissue mass and irregular erosion of the ends of the tibia and fibula. Re amputation through the lower third of the femur was performed. Examination showed a large mass of hard fibrous tissue enveloping the bone ends and infiltrating the muscles and skin. Microscopically a densely fibrous poorly cellular tissue like a hard fibroma.

Case II—History—In March 1925 a parous woman aged 65 noticed a small lump in her right calf. A year later when it had attained the size of a tennis ball it was excised. It was well defined, situated between the calf muscles and unattached to skin or bone. Microscopically it showed densely fibrous poorly cellular fibrous tissue and was diagnosed hard fibroma. The patient remained well for 18 months then late in 1927 recurrence of the growth was noticed. In May 1928 she first noticed a hard mass in her left lower abdominal wall, this slowly enlarged. In November 1929 when she was admitted to hospital the tumour in the calf had grown to a large size measuring 15 centimetres in length with commencing ulceration. The abdominal wall contained a large hard nodular mass unattached to the skin. In January the calf tumour underwent rapid ulceration and death occurred in February 1930 at the age of 70. *Necropsy*—Extensive ulcerated soft growth of right calf replacing muscles but unattached to bone, no metastases. Lobulated hard fibrous mass 10 centimetres in diameter superficial to but adherent to the aponeurosis and muscles of the left lower abdominal wall. *Histology*—Calf tumour consisted partly of well differentiated fibroma like tissue partly of undifferentiated sarcoma with many large irregular and multinucleated cells. Abdominal tumour was a densely fibrous partly hyaline poorly cellular fibroma.

These cases show that seemingly benign fibromatous structure is compatible with malignant growth properties. In most cases however the structure of malignant fibroblastic tumours accords with their behaviour, some degree of cellular anaplasia is present and mitotic figures are easily found. The main risk of such tumours is metastasis by the blood stream to the lungs and elsewhere. Metastases in lymph glands, as in cases reported by Warren and Meyer are relatively infrequent.

The behaviour of fibroblastic tumours differs with their sites of origin justifying separate consideration of the several regional groups of growths now to be described.

(3) Fibroblastic tumours of nerve sheaths

Chapter 54 gives an account of nerve sheath tumours and of the controversy regarding their histogenesis. This need not concern us here. Suffice it that there do occur tumours of nerves—neurofibromas and neurofibrosarcomas—which consist wholly or predominantly of collagen forming fibroblastic tissue and that probably many fibroblastic tumours not demonstrably related to nerves are nevertheless of nerve sheath origin (Stewart and Copeland). The ground for this second assumption is that the more thoroughly fibromas and fibrosarcomas of doubtful origin are examined the more often evidence of their relation to nerves is detected. Such evidence comprises the entry of recognizable nerves into the tumour, the presence of medullated or non medullated nerve fibres within the tumour, or extensions of tumour tissue along nerves marginal to it. Whorling and myxoid change are also suggestive but not conclusive. Deliberate search for these features in fibroblastic growths will sometimes establish beyond reasonable doubt their neurofibromatous nature. However it is a mistake to assume

polyps and "juvenile nasopharyngeal fibromas" continue to figure in many text books as tumours. The tendency of these lesions to recur, to spread over

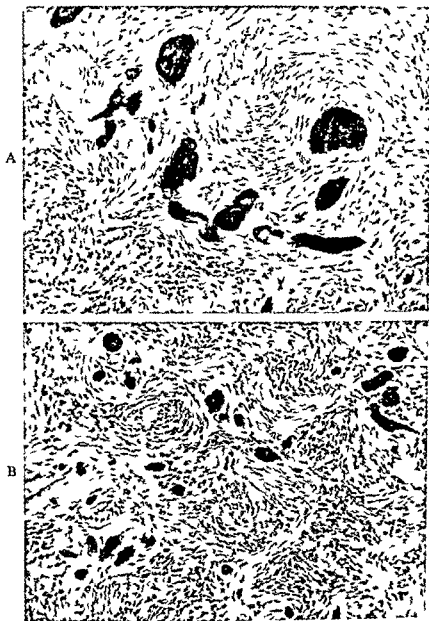


FIG 318—Case III. Fibroma of the maxilla with calcified foci. A = upper part of tumour where the calcified foci are clearly derived from included residues of bone. B = central part where whorled structure and calcified spherules simulate meningioma. (Cp Fig 320) ($\times 120$)

a wide field of diseased mucosa and to lead to infective complications in adjacent cavities, bones and other tissues, has given them a false clinical reputation of neoplastic qualities. The nature of the rare "malignant granuloma" of the nasal cavity is also open to doubt, the cytology and destructive invasiveness of

kilograms in one case and recurrence may follow incomplete removal. In spite of these features, the tumours are not malignant, neither metastasis nor microscopic evidence of sarcomatous change has been recorded. Large tumours undergo mucoid or cystic degeneration and may rapidly increase in size from imbibition of fluid; this must not be mistaken clinically for malignant change. While it may well be that the coexistence of a fibroma of the abdominal wall and a fibrosarcoma of the calf in my Case II above was fortuitous, the possible existence of a general predisposition to fibroblastic neoplasia must also be admitted.

(6) Fibroblastic tumours of bones

Cappell described an endosteal fibroma of the fibula from a man of 32 years and Jaffe and Lichtenstein described 10 similar growths in the shafts of long bones in patients from 6 to 21 years old of both sexes. All of these tumours proved to be benign but that some central fibroblastic tumours of bones are malignant is shown by my Case I above. According to Stewart and Copeland, parosteal fibrosarcomas are often of neural origin and associated with stigmata of neurofibromatosis. Peers described an endosteal neurogenic sarcoma of the ulna. Steiner saw a remarkable case of multiple diffuse fibrosarcomas of many bones.

Fibromas of the jaws, distending the bones or filling the maxillary antrum, have been well described by Boemke Giessen and the following example deserves record.

Case III—A man aged 26 years had noticed a gradually increasing swelling of the left side of his face for 7 years. This had been variously diagnosed as dental cyst, osteoma and leontiasis. Skiagrams showed opacity and distension of the antrum with erosion of its inferior and lateral walls. A biopsy specimen showed fibromatous tissue of benign appearance and operative removal was therefore undertaken. The large tumour was found to spring from the floor of the antrum which it filled and distended. The upper surface of the growth stripped away smoothly from the orbital wall but parts of the palate and nasal wall had to be removed in order to effect its complete removal. Over 70 grammes of tumour tissue were removed. *Histology* (Fig. 318).—It was a well differentiated fibrous tumour of moderate cellularity but with few or no mitotic figures, partly clothed on its upper surface by a bony shell and containing scattered rounded or elongated calcified granules. These probably developed from residues of necrotic bone spicules included in the tumour. Continuity of the calcified masses with fragments of bone was evident in the upper portion of the growth. *Progress*.—There was no evidence of recurrence 18 months later.

The attachments of the growth and the presence of a shell of bone on its upper surface in this case show that it arose in the maxilla and pushed the bony floor of the antrum upwards as it expanded into this cavity. The scattered calcification in the tumour closely resembled that described by Boemke Giessen and that present in the nasal fibroma in dog No. 4 below. It is evidently a special feature of fibromas of this region.

(7) Nasal and nasopharyngeal fibroblastic tumours

While true fibroblastic tumours of the nasal and nasopharyngeal mucosa may rarely occur, most of the so-called fibromas and myxomas are not neoplasms but inflammatory or allergic overgrowths. It is regrettable that nasal

tumours—rarer than oedematous fibromas, with which they must not be confused. Only the demonstration of mucin justifies the diagnosis of myxoma (Fig 319). Fibroblastic tumours of nerve sheath origin, especially the malignant ones, are particularly liable to partial myxomatous change. Most of the few myxomatous growths which I have examined showed structural evidence of a nerve sheath origin or were from situations which suggested the likelihood of such an origin.

Intercellular mucin may appear also in mesenchymal tumours of other kinds, especially cartilaginous and adipose tumours (q v). Sylvén has advanced the idea that mucinous change in mesenchymal tumours is a manifestation of proteolytic activity of the tumour cells and is related to their invasiveness, but the evidence is unconvincing.

Most prominently myxomatous tumours are to be regarded as malignant, in that they are prone to recur after attempted removal and eventually to metastasize. The attempt to distinguish benign myxomas and myxosarcomas is even more futile than with their collagenous counterparts.

Endocardial myxomas and pseudo-myxomas

For good accounts of these, see Yater, Muller and Fawcett and Ward. They are rare polypoid growths which spring from the endocardium usually of the left atrium. As Muller pointed out, diverse lesions have been placed in this group, including true endocardial tumours, tumours of the heart wall invading the chambers, and unorganized or organizing thrombi. Often, although the growths may have a myxomatous appearance to the naked eye, special stains have failed to confirm the presence of mucin (Muller), but in other tumours, as in that described by Orr, abundant mucin has been present. There is no doubt that, while oedematous organizing thrombi have sometimes been mistaken for tumours, there are genuine endocardial fibroblastic neoplasms with a tendency to mucinous change. Orr's view that the tumours are "essentially endotheliomatous" is, I think, unnecessary, and his comparison of them with the so-called 'mixed' salivary tumours, which are simple epithelial growths, is unfortunate. Most of the reported tumours have been non-invasive and benign, but in Muller's first case, the tumour diagnosed as a fine-fibred fibrosarcoma had produced metastases in the lungs. A small tumour of the aortic valve described by Yater as a "papilloma" consisted of a bunch of fine endocardial villi clothed by endothelium.

FIBROBLASTIC AND MYXOMATOUS TUMOURS IN ANIMALS

Fibroblastic tumours are commoner in many species of animals than in man. Feldman's Chapters IV and V and Chapter 6 of this book give many references to fibromas, fibrosarcomas and myxomas in horse, cattle, swine, dogs, cats, rodents, birds, reptiles and fish. In their range of structure and behaviour these growths resemble the human ones, and some of them show similar evidence of origin from nerve sheaths.

Not including a number of spindle-celled and pleomorphic-celled sarcomas which were probably fibroblastic but were too undifferentiated for certain

this lesion certainly suggest, but do not conclusively prove, that it is a malignant tumour

(8) Fibromas of the ovary

Excluding the cortical fibro papillary tumours in which both surface epithelium and fibrous stroma participate fibromas of the ovary usually arise not from the simple fibroblastic framework of the organ but from its undifferentiated mesenchyme which is its peculiar parenchyma (see Chapter 29) Granulosa cell theca cell and luteal cell tumours are all related ovarian follicle tumours and most or all fibromas are of the same group representing the most matured



FIG 319 —Myxosarcoma From a subcutaneous mucin rich tumour 8 centimetres in diameter noticed growing for 9 months in abdominal wall of a woman of 61 years ($\times 170$)

end product of the series just as the corpus fibrosum is the end product of the maturation of the normal follicle

PREDOMINANTLY MUCINOUS TUMOURS MYXOMA AND MYXOSARCOMA

Just as for the histologist the presence of intercellular mucin is the only feature distinguishing mucoid from collagenous connective tissue, so for the pathologist this is the only feature distinguishing myxomas from fibromas There is no such cell as a myxoblast distinct from a fibroblast The formation of mucin in the matrix of young mesenchymal tissue is widespread in the embryo and re appearance of this property in some fibroblastic growths is not surprising Myxomas and myxosarcomas are then merely fibromas and fibrosarcomas in which mucin has developed in the intercellular matrix They are relatively rare

mingled with the normal structures of the affected part, which may show other developmental anomalies also, such as deformation of bones and muscles or angiomas. Doubtless, some of these congenital "lipomas" are not true tumours, but hamartomas—superfluous tumour like masses of improperly blended tissues, comparable with most "angiomas", and without powers of disproportionate progressive growth. In many other cases, however, the tumours do grow progressively and attain large sizes, thus displaying their neoplastic qualities. The following examples from the voluminous literature will exemplify the range of situation and structure of these interesting growths.

Butlin removed a large well circumscribed encapsulated tumour from deep in the calf and interosseous space of the leg of a child aged 7 years. The tumour had been noticed since the child's first year and had grown steadily. Microscopically it showed adipose and fibrous tissue in about equal amounts, it contained also many striated muscle fibres which could be traced into the growth from its capsule and which had probably been enclosed in the tumour as it grew and were not of new formation (Cf Cases III and IV below).

Lockwood described bilateral congenital fatty tumours of the feet, and a congenital lipoma of the palm of the hand, Powers, a congenital fatty tumour connected with the periosteum of the femur, and Bland Sutton depicted and referred to similar cases. Eve described an unusually large congenital lipoma, weighing 3½ pounds, removed from the abdominal wall of a girl of 13 years. Adair and co workers described a child with Fröhlich's syndrome and congenital lipomas of the hand and arm, a negro girl with large multiple tumours of the forearm, arm, axilla and shoulder, accompanied by deformities of the limb bones, and an infant 5 months old with diffuse lipomatosis of a lower limb accompanied by two cavernous angiomas of the same limb.

Baker and Adams described multiple lipomas of the choroid plexus, base of the brain and spinal canal in a hydrocephalic female infant who also had defects of the skull, xanthomas of the eyelids and malformed irises. These writers reviewed reports of similar cases, which showed other associated malformations including agenesis of the corpus callosum, absence of the kidney, hare lip and cleft palate. (On lipomas of the central nervous system see also Kramer.) Large masses of fat, often called "lipomas", may overlie spina bifida or meningocele.

The following personally studied case affords an interesting example of the admixture of congenital lipomatous tissue with the structures of the part.

Case I—A healthy female infant 5 months old had had a swelling below the right angle of the mandible since birth with slight increase in size since. It was easily enucleated and proved to be a well defined nearly spherical slightly lobulated mass 4.2 centimetres in diameter 19 grammes in weight. On section it appeared to consist of firm pale adipose tissue throughout. Microscopical examination of many sections showed everywhere the same structure namely fully differentiated adipose tissue containing also plentiful glandular tissue consisting of branching ducts and relatively scanty simple acini (Figs 321 and 322). Some compressed parotid tissue was attached to the capsule of the tumour and it was clear that the glandular elements in the tumour consisted of salivary tissue which had been incorporated within a congenital lipoma.

diagnosis Rudduck and I examined the following fibroblastic tumours from animals

No	Animal	Tumour	Necropsy findings
1	Dog	- Fibroma (? neurofibroma) of skin of hock	—
2	Dog	- Fibroma of vagina	—
3	Dog	- Fibro sarcoma of skin of neck	Metastases in lymph glands lungs pleura heart liver kidneys
4	Dog	- Fibrosarcoma of nasal cavity (Fig 320)	Huge tumour 11 centimetres in main diam ter with granular calcification (cp Case III above) No metastases
5	Dog	- Fibrosarcoma of mediastinum	Metastases in lungs heart liver peritoneum
6	Dog	- Fibrosarcoma of neck	No metastases
7	Dog	- Fibrosarcoma of skin of thigh	Metastases in lymph glands
8	Dog	- Fibrosarcoma of skin of chest	—
9	Cat	- Fibrosarcoma of skin of foot	—
10	Cat	- Neurofibrosarcoma of foot	No metastases
11	Horse	- Neurofibroma of skin of buttock	—
12	Horse	- Fibrosarcoma of skin of fetlock	—
13	Parakeet	- Myxoma of subcutaneous tissue near wing base	—



FIG 320 —Nasal fibroma with focal calcification from a dog (Cp Fig 318) ($\times 120$)

Notable points are that at least 8 of the 13 tumours were from the skin or subcutaneous tissues that at least 3 were of neural origin, and that fibrosarcomatous metastases in lymph glands were present in 2 cases

mingled with the normal structures of the affected part, which may show other developmental anomalies also, such as deformation of bones and muscles or angiomas. Doubtless, some of these congenital "lipomas" are not true tumours, but hamartomas—superfluous tumour like masses of improperly blended tissues, comparable with most "angiomas", and without powers of disproportionate progressive growth. In many other cases, however, the tumours do grow progressively and attain large sizes, thus displaying their neoplastic qualities. The following examples from the voluminous literature will exemplify the range of situation and structure of these interesting growths.

Butlin removed a large well circumscribed encapsulated tumour from deep in the calf and interosseous space of the leg of a child aged 7 years. The tumour had been noticed since the child's first year and had grown steadily. Microscopically it showed adipose and fibrous tissue in about equal amounts, it contained also many striated muscle fibres which could be traced into the growth from its capsule and which had probably been enclosed in the tumour as it grew and were not of new formation. (Cf Cases III and IV below.)

Lockwood described bilateral congenital fatty tumours of the feet, and a congenital lipoma of the palm of the hand, Powers a congenital fatty tumour connected with the periosteum of the femur and Blind Sutton depicted and referred to similar cases. Eve described an unusually large congenital lipoma weighing 3½ pounds, removed from the abdominal wall of a girl of 13 years. Adair and co workers described a child with Frohlich's syndrome and congenital lipomas of the hand and arm, a negro girl with large multiple tumours of the forearm, arm, axilla and shoulder, accompanied by deformities of the limb bones, and an infant 5 months old with diffuse lipomatosis of a lower limb, accompanied by two cavernous angiomas of the same limb.

Baker and Adams described multiple lipomas of the choroid plexus, base of the brain and spinal canal in a hydrocephalic female infant who also had defects of the skull, xanthomas of the eyelids and malformed irises. These writers reviewed reports of similar cases, which showed other associated malformations including agenesis of the corpus callosum, absence of the kidney, hare lip and cleft palate. (On lipomas of the central nervous system, see also Krainer.) Large masses of fat, often called "lipomas" may overlie spina bifida or meningocele.

The following personally studied case affords an interesting example of the admixture of congenital lipomatous tissue with the structures of the part.

Case I—A healthy female infant 5 months old had had a swelling below the right angle of the mandible since birth, with slight increase in size since. It was easily enucleated and proved to be a well defined, nearly spherical, slightly lobulated mass 4.2 centimetres in diameter, 19 grammes in weight. On section it appeared to consist of firm, pale adipose tissue throughout. Microscopical examination of many sections showed everywhere the same structure, namely fully differentiated adipose tissue containing also plentiful glandular tissue consisting of branching ducts and relatively scanty simple acini (Figs 321 and 322). Some compressed parotid tissue was attached to the capsule of the tumour and it was clear that the glandular elements in the tumour consisted of salivary tissue which had been incorporated within a congenital lipoma.

BENIGN LIPOMAS AND FIBRO LIPOMAS OF ADULTS

I propose to say little of the clinical characters and gross structure of these, which are sufficiently described in most text books



FIG 321 —*Case I* Congenital lipoma with included parotid glandular tissue ($\times 41$)

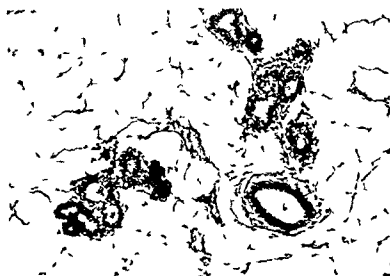


FIG 322 —Detail of Fig 321 ($\times 120$)

(1) Age, sex, site and number

While no age is exempt most lipomas develop in middle aged or elderly people the mean age in 23 cases which I have seen was 52 years The mean age in Adair's and co authors series was 41 years but these included congenital as

well as adult cases. Since many patients have had their tumours for several years before undergoing operation, the mean age of actual onset must be considerably less than that usually recorded. Although Adair and co authors found that 73 per cent of lipomas were in females, it is doubtful if this obtains generally, of my 23 cases, 12 were women and 11 were men. The commonest sites are the subcutaneous tissues of the limbs or trunk, and the retroperitoneal tissues and inguinal canal. Submucous lipomas of the larynx, oesophagus, stomach or intestine, and lipomas of solid viscera, are rare. Most lipomas are solitary, two or three tumours are not unusual, numerous multiple ones are rare. Adair *et al* described a man with 160 subcutaneous lipomas. There are good grounds for regarding the cases with many lipomas as belonging to a distinct and peculiar group (*see below*). Lipomas may attain huge dimensions, the largest recorded being the retroperitoneal lipoma reported by Delamater (cited and depicted by Stout) which weighed at least 179 pounds and possibly 275 pounds.

(2) Causation

(a) *Congenital predisposition*

The remarkable characters and variety of the congenital lipomas, described above, have led Ewing and others to postulate a "congenital tissue predisposition" for lipomas generally. Support for this view is afforded by the occasional instances of an *heredo familial predisposition*. Thus Adair *et al* described a woman 53 years old who had 16 subcutaneous lipomas, and whose two sons and a grandson also had multiple lipomas, and these writers refer to other records of familial cases. However it is very doubtful if any congenital predisposition obtains for the ordinary solitary lipomas appearing during adult life. These are probably unrelated to the congenital tumours, and they show no significant familial incidence.

(b) *Relation to the nervous system*

Adair and co workers have advanced reasons for believing multiple lipomas to be related to disturbances of innervation. Thus, these tumours show many points of similarity to neurofibromatosis—namely, their usual appearance in adolescents or young adults, their symmetrical distribution, the presence of sensory or trophic disturbances in some cases, of skin pigmentation in some cases, of an hereditary tendency, and the occasional coexistence of lipomas and neurofibromatosis. Adair *et al* also thought it probable that congenital lipomas may be related to nerves or to disturbed innervation. Hueper refers to cases of acquired multiple lipomatosis associated with injury or disease of the spinal cord or nerves. There is need of further careful structural studies of congenital and acquired multiple lipomas and their possible relation to peripheral nerves or to disease of the central nervous system.

(c) *Trauma*

Ewing and others have supposed trauma to play a part in the genesis of lipomas and liposarcomas, but except for the rare instances of multiple lipomas associated with spinal injuries, there is no substantial evidence for this view.

BENIGN LIPOMAS AND FIBRO LIPOMAS OF ADULTS

I propose to say little of the clinical characters and gross structure of these, which are sufficiently described in most text books



FIG 321 —Case 1 Congenital lipoma with included parotid glandular tissue ($\times 41$)

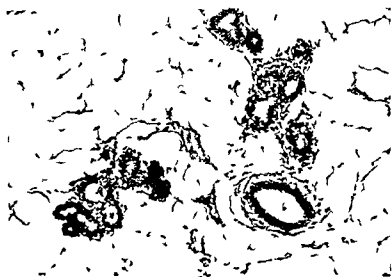


FIG 322 —Detail of Fig 321 ($\times 120$)

(1) Age, sex, site and number

While no age is exempt, most lipomas develop in middle aged or elderly people the mean age in 23 cases which I have seen was 52 years The mean age in Adair's and co authors series was 41 years but these included congenital as

the malignant part of the growth is a fibrosarcoma, not a liposarcoma (Fig 326) The term "liposarcoma" should be applied only to tumours whose cells are malignant lipoblasts

Further caution is needed before dubbing a tumour "liposarcoma" just because it contains fat laden cells Many kinds of anaplastic tumours show tumour cells with fat or lipid droplets due to degenerative changes, and of course macrophages laden with such materials are often plentiful in tumours When dealing with a cellular tumour of uncertain nature, which might be a liposarcoma, all other possibilities must be considered, and the diagnosis must sometimes remain uncertain unless complete necropsy has proved the absence of an unsuspected primary growth of other nature elsewhere Some cases reported as "liposarcoma" (e.g. Stewart's case 2) are open to doubt on these grounds



FIG 326—From a myxosarcomatous part of a large retroperitoneal lipoma in a man aged 47 ($\times 400$)

True malignant tumours of adipose tissue are rare The best recent account of them is that of Stout, which contains some good examples and many references Most of them develop in middle aged or elderly people The sexes are about equally liable Trauma is of very doubtful influence in causation The principal sites are the lower limb, retroperitoneal tissues and inguinal canal, but no site is exempt Most liposarcomas of the limbs appear to arise deeply in intermuscular or intramuscular positions rather than in the subcutaneous tissues There are several well attested cases of malignant change in pre existing benign lipomas (Adair *et al*, Stout)

(1) Structure

Liposarcomas show very variable rates of growth and degrees of histological differentiation and it seems probable that as with most other classes of tumours, sharp distinction between lipoma and liposarcoma is not always possible, and that borderline tumours occur Malignancy should be suspected if an apparently

Trauma was seldom noted in Adair and co workers' series or in my own series of 23 lipoma cases and Stout's 41 cases of liposarcoma gave no histories of significant trauma

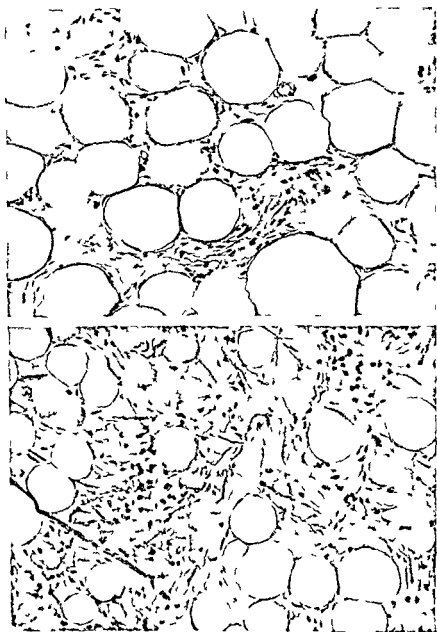


FIG 323 —Case II Scrotal fibro lipoma ($\times 120$)

(3) Structure

Many lipomas consist of fully mature fat cells arranged in lobules with a variable amount of supporting connective tissue and blood vessels. Two not unusual structural features however require special comment namely (a)

experimental production of tumours of adipose rather than of fibroblastic elements by carcinogens

TUMOURS OF ADIPOSE TISSUE IN ANIMALS

Lipomas are well known to occur in almost all kinds of domestic animals. Feldman gives examples and cites many recorded lipomas in horses, cattle, swine, sheep, dogs and birds. Of interest in showing points of similarity to human tumours are the instances of multiple subcutaneous and intermuscular lipomas in horses, the intestinal lipomas of horses, the congenital lipoma of the skull of a calf reported by McFadyean, the probably congenital lipoma of the brain reported by Kuhnau, and the large intracranial lipoma in a hog examined by Feldman. As in man, so in the larger animals lipomas may attain a huge size, Feldman mentions a horse tumour weighing 42 kilograms. Microscopically, animal lipomas consist of mature fat cells or of mixtures of these with immature lipoblasts. Fibro lipomas with admixed fibrous tissue also occur. Feldman gives no specific instances of liposarcoma.

Rudduck and I collected the following lipomas from animals: (a) a lipoma 10 centimetres in diameter and 450 grammes in weight, removed surgically from the subcutaneous tissue of the perineum of a female cattle dog 6 years old, (b) two lipomas, one 4.5 centimetres and the other 8 centimetres in diameter, removed surgically from the perineum of an adult female Pekinese, (c) a pedunculated ovoid subcutaneous lipoma 5 centimetres in main diameter, which had been growing slowly for 3 years on the inner aspect of the thigh of an adult parrot.

REFERENCES

- Ackerman, L. V. (1944) *Amer J Path* 20 789
 ADAIR, F. E., PACK, G. T., and FARRIOR, J. H. (1932) Lipomas *Amer J Cancer* 16 1104 (An interesting well illustrated paper)
 Baker, A. B. and Adams, J. M. (1938) *Amer J Cancer*, 34 214
 Bland Sutton, J. (1906) *Tumours Innocent and Malignant* Chapter I London
 Butlin, H. T. (1877) *Trans Path Soc Lond* 28 221
 Eve, F. S. (1888) *Trans Path Soc Lond* 39 295
 Ewing, J. (1940) *Neoplastic Diseases*, Chapter XII Philadelphia
 Feldman, W. H. (1932) *Neoplasms of Domesticated Animals* Chapter VIII Philadelphia
 Gernet, E. (1867) *Virchows Arch* 41 534
 Haagensen, C. D., and Krehbiel, O. F. (1936) *Amer J Cancer*, 27, 474
 Hueper, W. C. (1942) *Occupational Tumors* p 660 Springfield
 Jaffe, R. H. (1926) *Arch Path* 1 381
 Krauer, L. (1935) *Virchows Arch* 295 107
 Lockwood, C. B. (1886) *Trans Path Soc Lond* 37 450
 Mallory, F. B. (1923) *Principles of Pathologic Histology* p 301 Philadelphia
 Murray, M. R. and Stout, A. P. (1943) *Amer J Path* 19, 751
 Nienhuis, J. H. (1925) *Z Krebsforsch* 22 434
 Power, D. A. (1888) *Trans. Path Soc Lond* 39 270
 Seids, J. V., and McGinnis, R. S. (1927) *Surg Gyn Obst* 44 232
 Siegmund, H. (1934) *Virchows Arch* 293 458
 Stewart, F. W. (1931) *Amer J Path* 7 87
 STOUT, A. P. (1944) Liposarcoma—the malignant tumor of lipoblasts, *Ann Surg* 119, 86 (A well illustrated paper with many references)
 Virchow, R. (1865) *Virchows Arch*, 32 545
 Waldeyer, W. (1865) *Virchows Arch* 32 543
 Wells, H. G. (1940) *J Amer Med Assoc* 114 2177 2284

lipomatous tumour shows unusual variations of texture or colour and especially if it contains mucoid areas

Microscopic structure

This is very variable from fully differentiated adipose tissue cells to completely anaplastic cellular sarcoma and often includes also areas resembling myxoma or immature mesenchymal tissue. All cellular variants may be found in different parts of one tumour. Immature and giant lipoblasts showing all stages of vacuolation are common. Fat stains applied to frozen sections will of course give the best pictures of the contents of mature or maturing cells. Subdivisions of liposarcomas according to their microscopical characters is unwarranted. Stout gives good illustrations of the variety of structure and stresses the impossibility of histological sub division of the group. Murray and Stout describe the characters of malignant lipoblasts in tissue culture.

Certain features in the structure of lipomas and liposarcomas bear on the problem of the histogenesis of adipose tissue. We have seen—(a) that lipomas are often fibro lipomas, (b) that the fibromatous component may become a malignant fibrosarcoma (c) that the lipomatous component may become a malignant liposarcoma (d) that the structure of liposarcoma is highly variable and often includes mesenchyme like or myxoid tissue. These observations strongly suggest that while under normal conditions fat cells or their precursors may preserve their specialized functions and structure in pathological proliferations such as tumours they may display more diverse capacities for differentiation. Although tumours seldom appear to contain cells of transitional type between fibroblasts and lipoblasts it is nevertheless not unlikely that the proliferation in tumours may involve de differentiation of cells to a functionally indifferent level and their redifferentiation in part along divergent lines.

(2) Multiplicity and metastasis

In view of the multiplicity of lipomas in some cases it is not surprising that liposarcomas also may be multiple and in some cases with multiple tumours, it has been debatable whether these were independent primary growths or metastases. Stout and Ackerman give examples of probable multiplicity and refer to others. Siegmund described a remarkable case of widespread liposarcomatous tumours of the subcutis retroperitoneal tissues mediastinum, bone marrow and other parts in a woman aged 65 and he regarded the condition no doubt correctly as a system disease of adipose tissue throughout the body.

Metastasis from liposarcoma certainly occurs however—to the lungs liver bones brain and other organs as in cases reported by Waldyer Virchow Gernet, Nienhuis Jaffe Seids and McGinnis Ewing and Stout.

(3) Experimental production of liposarcoma

Hjartensen and Krehbiel obtained liposarcomas in a mouse and four guinea pigs following subcutaneous injections of benzpyrene. Further experiments are needed to elucidate the local or constitutional conditions necessary for the

(2) Intermutability of cell-types in the skeleton

The intermutability of various types of cells of mesenchymal origin, already discussed in Chapter 41, must be re emphasized here. Skeletal fibroblasts, chondroblasts, osteoblasts and osteoclasts are not distinct immutable species of cells, but can readily undergo metaplastic transformations one to another in many kinds of pathological states. Indeed, some of these transformations take place normally or in simple repair, the formation of new bone by the fibrous periosteum and of cartilage by the perichondrium may be looked on as physiological metaplasias. The structure of perichondrium is particularly notable in this respect, this membrane shows a gentle transition from fibrocytes to cartilage cells. Of course, extra skeletal connective tissues also can undergo bony or cartilaginous metaplasia, periosteal and perichondria merely exhibit to a special degree this universal transformability of fibroblasts. The reverse transformation—of osteoblast to fibroblast—is also a frequent one, displayed in many familiar lesions in which the fibrous replacement of bone takes place, as in the various types of "osteitis fibrosa" and its congeners. In these lesions, the fibrous replacement is not effected by proliferation of pre existing fibroblasts to fill gaps left by departed bone cells, but by a progressive transformation of bone cells into fibrocytes. When re ossification of this fibrous tissue ensues, as in a recovering case of hyperparathyroidism, the fibroblasts again become functional osteoblasts.

We are too prone to think of osteoblasts and osteoclasts as distinct cells with distinct functions, rather than as functional variants of cells of the same type. Where these cells, by virtue of ambient conditions, are functionally concerned in laying down new bone or in actively maintaining bone already there, they are osteoblasts, where, by virtue of ambient conditions they are functionally concerned in bone resorption, they are osteoclasts. The osteoblast of to day may be an osteoclast to-morrow and vice versa, and this reversal of function probably amounts to no more than a slight alteration in the nature or quantities of the enzymes formed by the cells. In lesions with fluctuating deposition and resorption, there are many cells of borderline or 'neutral' appearance, which can be called "large osteoblasts" or "small osteoclasts" as one pleases.

(3) Intermutability of cell-types in skeletal tumours

The transformations seen in the normal growth of the skeleton and in its non neoplastic disturbances are seen also in its tumours. While it is true that some tumours show exclusive or predominant differentiation of one or another type—osseous cartilaginous, fibrous or osteoclastic—others show divergent differentiation resulting in variable admixtures of two or more of these. Chondromas ossify, cartilaginous or fibroblastic areas are found in osteogenic sarcomas, osteoclast like giant cells occur in osteogenic sarcomas and some tumours show the combined structure of osteoclastoma and chondroma. In an inbred strain of mice with a high incidence of skeletal tumours, Pybus and Miller found all types and combinations of growths—osteomas, osteosarcomas, chondrosarcomas spindle celled and giant celled tumours. Impartial survey of a collection of human skeletal tumours also shows the absence of sharp histogenetic subdivisions however necessary descriptive sub-divisions may be for clinical and

CHAPTER 43

TUMOURS OF CARTILAGE AND BONE

THE SKELETON contains a variety of tissues, including not only cartilage and bone but also fibrous tissue adipose tissue, haemopoietic cells and undifferentiated reticulo endothelial elements. The fibroblastic adipose and haemopoietic tumours of the skeleton are dealt with in other chapters, here we are concerned with tumours of osseous or cartilaginous tissue proper and with growths related to these. Before considering the particular kinds of tumours however, it is necessary to clarify certain general points regarding the structure and growth of the skeletal tissues and their tumours.

GENERAL CONSIDERATIONS

(1) The development of the skeleton

A knowledge of the normal development of bones and cartilages is essential to an understanding of their pathology including their tumours. Endochondral ossification, ossification in membrane periosteal bone formation osteoclastic resorption and modelling—all these familiar phenomena of normal growth have their counterparts in pathological growth. Hence, all that can be learnt of the normal development maintenance and metabolism of bone is sure to have a bearing on the pathology of its tumours. Indeed it is quite possible that the causes of most skeletal tumours will be found to be not externally introduced carcinogenic agents but disturbances of those factors on which the maintenance of bone depends—calcium and phosphorus vitamin D, parathormone and other hormones.

It is important to recall that the tissues of the skeleton do not attain maturity until adult life. Until the epiphyses unite endochondral ossification not essentially different from that of the foetus is still in progress. So also is periosteal ossification. This post natal persistence of skeletogenesis means persistence of foetal immaturity of the tissues and of their liability to malformations from interferences with their normal maturation. It is then theoretically possible that post natal as well as pre natal interferences may occasion heterotopic growth centres in epiphyseal or periosteal tissue and lead to the formation of exostoses or to abnormal persistence or aberrant differentiation of masses of cartilage.

The rates of growth and maturation of different parts of the skeleton are of interest to the pathologist. Disturbances of growth are likely to produce their major effects in parts which are most actively growing at the time and the pathological effects are likely to show gradients of severity corresponding to the growth gradients of the affected bone or of the whole skeleton if the disturbing factors are body wide. The distribution of many diseases of bone accords with this concept of greater susceptibility of the growing parts to injury. This applies not only to infections and deficiency diseases but also to tumours and tumour like malformations including enchondromas, exostoses giant-cell tumours and osteogenic sarcomas.

erroneously described as "cystic" may be produced by many diseases, including metastatic growths, osteolytic primary sarcoma, plasmocytoma chondroma, osteoclastoma, other central non osteogenic tumours such as fibrosarcoma or liposarcoma, and localized fibrocystic disease (Willis, 1938 Fig 9, Grout, Figs 4-7)

(d) *Confusion of primary and secondary multiple tumours*

The radiographic appearances of multiple myelomatosis and of disseminated carcinoma may be identical (Cosin, Willis)

Analysis of series of cases of bone tumours, the diagnoses of which have been based mainly on radiographic evidence, is valueless for pathological purposes

(6) *Classification adopted*

From what has been said, it will be clear that I am opposed to subdivisions of primary tumours of bone beyond those barely necessary, and that I regard even the main subdivisions adopted as arbitrary and of descriptive rather than histogenetic significance. The multiple exostoses and enchondroses are malformations, which though not true tumours, must be considered in relation to their solitary counterparts and to true enchondromas and osteomas. True enchondromas and chondrosarcomas cannot be separated, nor indeed can a sharp line be drawn between these and osteosarcomas. However, for descriptive purposes at least, it is convenient and useful to distinguish between predominantly cartilaginous and predominantly osteogenic sarcomas. The osteoclastomas form a fairly distinct group, which, however, as occasional malignant members and occasional members with combined chondromatous characters show, is not completely isolated. "Reticulum cell sarcoma" may be an entity or a distinct variant of primary sarcoma of bone, but too few cases have yet been investigated to warrant final conclusions. "Ewing's tumour" must be discussed, not because it is an entity, but because the name is still used frequently and indiscriminately.

We will consider the primary tumours peculiar to the skeleton under the following heads

- 1 Multiple enchondroses
- 2 Multiple exostoses
- 3 Solitary exostoses osteomas and osteochondromas
- 4 Solitary benign chondroma
- 5 Chondrosarcoma
- 6 Osteosarcoma
- 7 Osteoclastoma
- 8 Reticulum cell sarcoma of bone

To complete the list of possible primary tumours in bone, there must be added fibroma and fibrosarcoma, lipoma and liposarcoma, haemangioma, chordoma, solitary plasmocytoma, myelomatosis, myeloid leukaemia and Hodgkin's disease, all of which are considered elsewhere. In this chapter brief mention will be made also of bony and cartilaginous tumours of soft tissues

MULTIPLE ENCHONDROSES

I propose to say little of these rare malformations of the skeleton, for details of which the reader should consult the writings of Muller, Speiser, Stocks and

prognostic purposes. The names employed denote different predominant types of differentiation but not necessarily different specific tissue origins.

(4) Osteogenesis in non osteogenic tumours

Both pathologists and radiologists have often made the mistake of assuming that a tumour in which there is new formation of bone must be osteogenic. This fallacy is refuted by the osteoplasia and osteophytosis accompanying secondary carcinoma of bone and by the radiating osteophytes or parallel onion skin laminae of periosteal new bone in metastatic neuroblastoma (qv). These stromal reactions of bone and periosteum to invading non osteogenic growths are evident also in tumours of bone itself. In part at least the regular radiating spines of new bone accompanying periosteum expanding sarcomas of bone and the new bony laminae set at an angle to the shaft where the expanded periosteum meets it a feature often visible in skiagrams are products not of the tumour tissue but of the expanded periosteum. Brunschwig and Harmon (1935) studied these relationships in experimentally transplanted tumours in bone as well as in human material and concluded that much of the new bone seen in primary sarcomas of bones is indeed of non neoplastic periosteal origin a conclusion in which I concur (Willis 1938). However in osteogenic sarcomas it is sometimes impossible to distinguish with certainty between neoplastic and periosteal new bone and indeed where the periosteum is itself part of the tumour formative field the distinction ceases to exist.

(5) Limitations of radiographic diagnosis

Far too great a reliance has been placed on radiographic appearances in the diagnosis of tumours of bone. While these appearances often afford strong evidence of the nature of a tumour there are many possible fallacies. Experienced radiologists are well aware of these and are the first to deplore the prevalent assumption that radiologists possess clairvoyant powers for radiographic shadows. It cannot be too strongly insisted that for purposes of precise diagnosis classification and research microscopical study of adequate pieces of tumour is essential. There may be—there are of course—limits to the practicability of attaining this ideal in all cases but in so far as it cannot be attained diagnosis must necessarily remain uncertain.

Possible errors in the radiographic diagnosis of bone tumours commented on in my 1938 paper and particularly dealt with by Grout include the following.

(a) *The assumption that osteogenesis implies an osteogenic tumour*

This has been dealt with above (see also Grout's figures 1, 2 and 3). It is the main cause for mistaking secondary growths for primary ones.

(b) *Calcification may be mistaken for ossification*

Chondromas, chondrosarcomas or chordomas containing calcified areas may be mistaken for osteosarcomas.

(c) *Confusion of solitary lesions producing well circumscribed bone destruction*

Circumscribed destruction producing radiographic appearances often

identified radiographically at birth and in infants. They progress at varying rates during the growing period, during which they possess growing caps of cartilage which undergo ossification *pari passu*. When growth of the skeleton ceases, the exostoses also cease to grow, and their cartilage caps become either completely ossified or reduced to a thin quiescent zone. The exostoses are not superimposed on the cortex of the bone but represent outpouchings of it with spongy bone within. In addition to the grossly obvious exostoses, affected bones show innumerable tiny excrescences and irregularities and often excessive width and abnormal contours. Diminished stature, bodily asymmetry or other deformities are sometimes present. The lesions tend to be symmetrically bilateral and are usually largest and most numerous in juxta epiphyseal parts of long bones, especially at the ends where main growth occurs, namely, the lower end of the femur, upper ends of tibia and fibula, upper end of humerus, and lower ends of radius and ulna. But the distribution varies greatly, and any chondral bones may be affected. In a high proportion of cases, about two thirds there is a definite family history of the disease. Stocks and Barrington found that in most cases inheritance was through an affected parent, the father about three times as frequently as the mother. Transmission sometimes occurred through an unaffected female but apparently not through an unaffected male. About two thirds of the subjects with multiple exostoses are males.

The disease is clearly a general disturbance of ossification in cartilage bones. Controversy as to whether this disturbance affects chiefly the periosteum or the epiphyseal cartilages is I think, pointless. Keith's concept of a general defect of modelling of the bones (diaphyseal achisis) can embrace both.

Chondrosarcoma supervening on multiple exostoses

One of the first reports was that of Weber (1866), who described a man of 25 years with multiple exostoses and a large chondrosarcoma of the pelvis which had invaded the iliac vein and produced cartilaginous emboli in the pulmonary arteries. Jaffe reported 3 cases of chondrosarcoma in his series of 28 cases of multiple exostoses (11 per cent) but pointed out that since most of these patients were children or adolescents and since sarcoma usually does not supervene until adult life (at 25, 28 and 36 years in his 3 cases) the final proportion of cases to develop sarcoma must certainly be greater than 11 per cent. However, sarcoma does occasionally develop even during childhood, e.g. at the age of 10 years in Bennett and Berkheimer's case.

Sarcomas supervening on multiple exostoses appear always to be chondrosarcomas usually of the well differentiated gelatinous type apt to be microscopically diagnosed as soft "chondroma" (see below). These tumours are often of slow growth: they may grow to huge sizes locally without metastasizing as in Jaffe's second case of 13 years' duration or they may invade veins and disseminate to the lungs and elsewhere, as in Weber's case.

SOLITARY EXOSTOSES, OSTEOMAS AND OSTEOCHONDROMAS

Solitary growths generally similar in structure to those of hereditary multiple exostoses are the commonest tumours of the skeleton. Like the multiple lesions,

Barrington Cole, Hunter and Wiles and Jacobson The disease variously known as 'multiple enchondromata enchondromatosis' 'dyschondroplasia' (Ollier), and 'chondrodysplasia', is characterized by the presence from an early age of masses of cartilage within many or all of the cartilage bones of the body especially of the limbs The lesions may be symmetrical or asymmetrical and they vary considerably in their bulk and the degree of deformity they produce There is no justification for separating as 'Ollier's disease' only cases showing asymmetry even though the cases described by Ollier were of this kind

Speiser's full necropsy study of this disease in a boy of 4 years showed that many of the masses of cartilage within the diaphyses of long bones had pedicles of attachment to the epiphyseal cartilages, but that others were unrelated to these and arose from islands of cartilage in the periosteum These findings show that the controversy as to whether the 'chondromas' arise from the epiphyseal cartilage or periosteum is pointless they arise from both as a result of some general disturbance of ossification in cartilage The presence of periosteal islands of cartilage in this disease similar to those described by Muller and others in cases of multiple exostoses suggests a relationship between the two diseases, and some writers have assumed that they are but different manifestations of one disease There is very little real evidence to support this view with rare and doubtful exceptions patients show either exostoses or enchondroses and not both (Jaffe), and while a familial incidence obtains for the majority of cases of multiple exostoses this is exceptional in cases of pure enchondromatosis (Stocks and Barrington Jacobson) The supposition that the two diseases are related and that they are seen in combination in individuals and in families appears to be in part at least due to incomplete observations

With the lapse of time most of the cartilaginous masses in patients with enchondromatosis become quiescent and they may undergo regression or ossification But some during or after the period of normal growth of cartilage continue to grow excessively as true chondromas or chondrosarcomas (references by Hunter and Wiles) It is difficult to deny the neoplastic quality of the huge multiple masses of cartilage which develop in the hands and feet and elsewhere in some cases (figures of which are reproduced by Stocks and Barrington) 'Typically and essentially however enchondromatosis is a dystrophic and not a neoplastic disease (Jacobson) Speiser advanced reasons for believing that the initial disturbances leading to this disease operate between the fourth and eighth months of foetal life

MULTIPLE EXOSTOSES

This familiar disease designated also multiple ossifying chondromata diaphyseal aclasis (Keith) and hereditary deforming chondrodysplasia (a vague clumsy name) also calls for no more than summary treatment here Details will be found in the papers of Muller Keith Stocks and Barrington Jacobson and Jaffe

Like enchondroses multiple exostoses are malformations not neoplasms Although they are often not discovered until later childhood or adolescence they probably take origin in most cases during foetal life for they have been

particularly stressing the histological features which suggest malignant properties, and also the grounds for distinguishing between chondrosarcoma and osteosarcoma

(1) Age and sex

On the average, chondrosarcomas arise much later in life than osteosarcomas. Most patients are between 30 and 50 years old, and children are rarely affected. The sexes are about equally liable.

(2) Site and pre-existing lesions

The long bones of the limbs, the pelvis and the ribs are the most frequent sites. In roughly equal numbers of cases, the initial site of the tumour is central within a bone or springing from the surface of a bone or cartilage. In a small proportion



FIG. 328—Chondrosarcoma of upper half of humerus in a man of 41 years. At first diagnosed as a benign chondroma, the tumour recurred and metastasized to the lungs ($\times 60$)

of cases of central chondrosarcoma, this has supervened on a pre-existing supposedly benign enchondroma or enchondrosis. In a much larger proportion of cases of external chondrosarcoma of bone, this has arisen from a pre-existing cartilaginous exostosis or osteochondroma (Lichtenstein and Jaffe). There is insufficient evidence to incriminate trauma or any other specific factors in the causation of chondrosarcoma. The commonest of all cartilaginous tumours, those of the phalanges and metacarpals, are very rarely malignant, but a case with metastases was reported by Cruickshank.

(3) Structure

Some chondrosarcomas show plain histological evidence of malignancy—cellular pleomorphism, multinucleated cells, areas of spindle-celled growth and mitotic figures. Others consist wholly or mainly of well-differentiated, often soft mucoid cartilaginous tissue, microscopical study of which does not suggest

the solitary ones develop chiefly in young people, and affect chondral bones especially in juxta epiphyseal parts, and especially the lower end of the femur or the upper end of the tibia

The solitary growths are so similar to multiple exostoses in most respects, that there can be little doubt that they arise from a similar kind of developmental disturbance. In most cases however, this disturbance must be purely local for the remainder of the skeleton is normal and there is no clear evidence of an hereditary predisposition. Cases of apparently solitary exostosis are reported in families with multiple exostoses, but it is probable that complete examination



FIG. 327.—Case 1. Benign osteoid tumour of skull ($\times 120$)

of the skeleton in such cases would reveal other inconspicuous growths. Despite their similarity then the solitary growths should be regarded as distinct from the multiple ones and not merely as localized manifestations of the multiple disease. This distinction is all the more pertinent because the solitary growths not infrequently continue to grow after cessation of general growth of the skeleton thus showing their genuinely neoplastic character and their rightful claim to be called osteoma or 'osteochondroma' rather than exostosis. However the line of separation between neoplasm and malformation cannot be drawn with precision nor can we always distinguish between the strictly solitary growth and the seemingly solitary one which is the only manifestation of the hereditary disease. It is not unusual for a solitary osteochondroma to give origin to a chondrosarcoma.

Osteochondromas of the base of the skull are particularly described by List. The rare 'ivory' osteomas of the skull and facial bones form a peculiar group, the exact limits of which however it is difficult to define. When we have eliminated from the osteoma group—in which formerly they were often placed—such lesions as hyperostoses due to invading meningiomas, localized forms of leontiasis (the nature of which is still unknown), inflammatory

i.e. one-half of all tumours were close to the knee joint a proportion nearly identical with that in Christensen's series. Thus, the sites of predilection are, like those of exostoses and osteochondromas as well as of osteoclastomas, the ends of the long bones "where the growth period is longest, and the growth momentum is greatest" (Christensen). When a sarcoma arises in a bone with an ununited epiphysis, the primary site is in the diaphysis, primary epiphyseal sarcomas are excessively rare.

(3) Causation

The age and site incidence of osteosarcomas strongly suggests that their causation is to be sought mainly in disturbances of bone growth and maturation. This suggestion is supported by the analogous fact, already noted, that developmental enchondroses and exostoses certainly predispose to supervening chondrosarcoma, and by the occasional supervention of osteosarcoma in cases of fibrous dysplasia of bone (Albright's disease), as noted by Jaffe (1946). It must be noted here, however, that Albright's disease may itself produce large fibrous and cystic tumour-like masses which are to be regarded not as true neoplasms but as hamartomas.

(a) *Extrinsic carcinogens*

In only a very small fraction of cases of osteosarcoma is there evidence of extrinsic physical or chemical causative factors. Indeed, the only cases in which an extrinsic agent has been proved culpable are those due to absorbed *radio active substances*, as described in Martland's account of occupational osteosarcomas in watch dial painters. These tumours developed in young people after relatively brief periods of exposure. Thus the ages at necropsy of 5 cases reported by Martland were 20, 27, 30, 33 and 34 years, and the times of occupational exposure to radio active material were between one and five years. The tumours were multiple in 3 of the 5 cases and the sites included femur, scapula, vertebrae, pelvis and skull. Absorbed radium and other radio active elements accumulate in the skeleton and set up a chronic radiation osteitis and the evidence is clear that the sarcomatous change supervenes in areas of bone so affected. In cases of chronic poisoning by radio active substances, all but a minute fraction of the retained material is found in the bones. Chapter VII of Hueper's book contains an excellent outline of poisoning by radio active substances and of the osteosarcomas caused by them. The experimental production of bone sarcomas by means of radio active substances (see Chapter 4) has confirmed and amplified our knowledge of these tumours.

(b) *Trauma*

Injury has often been regarded as a cause of sarcomas of bone but the evidence is inconclusive. There do occur occasional cases, like that reported by Webster, in which sarcoma appears a few months or years after the infliction of an injury to the bone at the particular site but it is doubtful if these infrequent cases exemplify more than the laws of chance. The bones of all mankind receive frequent injuries, mild and severe, osteosarcomas are relatively rare tumours, the numerous fractures of modern life are very rarely followed by sarcoma, the great majority of cases of sarcoma give no clear history of trauma, and in not a

sarcomatous properties. As Lichtenstein and Jaffe insisted however thorough search of adequate material from such growths will often reveal areas with suspicious cellular atypism. Yet there are tumours the structure of which in both primary growth and metastases is indistinguishable from that of benign chondromas (Fig 328)

(4) Spread and metastasis

Many chondrosarcomas grow slowly remaining only locally invasive for years. Some tumours, however invade veins and metastasize to the lungs. Very extensive growth within large veins has been described by many writers e.g. by Weber, Ernst, Fry and Shattock, Kosa, Phemister and Warren. The tumours described by Fry and Shattock and by Kosa extended in continuity through the inferior vena cava and the right side of the heart into the pulmonary arteries. Blood borne metastases elsewhere than in the lungs are unusual but have been reported in bones (Recklinghausen, Martin), adrenal and heart (Lichtenstein and Jaffe), skin (Cruickshank) etc.

OSTEOSARCOMA

Osteogenic sarcomas—or more simply osteosarcomas—are those in which the tumour parenchyma displays recognizable differentiation of bone or osteoid tissue. As already pointed out the formation of new bone by expanded periosteum may be mistaken for bony differentiation in the tumour itself. But admitting this source of error it is still clear that many—indeed most—sarcomas of bone do themselves produce bone or osteoid tissue for these are often recognizable in extra periosteal extensions of the growths or in their metastases. A few sarcomas of bone are undifferentiated spindle celled or pleomorphic celled growths not microscopically identifiable as of bony origin. In my opinion sub division of the osteosarcomas into periosteal, medullary, sclerosing, telangiectatic etc. are artificial and unjustifiable. These adjectives do not denote distinct types of growth but merely variants of the one type.

(1) Age and sex

Christensen's analysis of 441 cases of bone sarcoma of all types (mainly of course osteogenic sarcoma) reveals the main features of age, sex and site incidence of this disease. Males are affected decidedly more frequently than females in a ratio of about 60 to 40 per cent. The greatest number of cases occurs in the second decade e.g. 40 of 80 cases reported by Badgley and Batts, nearly two thirds of all patients are between the ages of 10 and 30 and one third of them are over 30 years. Very young children and old people are seldom affected.

(2) Site

Christensen's figures showed that of the total of 441 tumours 287 (65 per cent) were in the lower limbs including 174 in the femur (162 at its lower end) and 83 in the tibia (69 at its upper end). 72 (16 per cent) were in the upper limbs, including 54 in the humerus (31 at its upper end) and 82 (19 per cent) were in the bones of the head and trunk, the commonest single site being the scapula. In Badgley and Batts's 80 cases there were 25 tumours of the lower end of the femur, 11 of the upper end of the tibia and 4 of the upper end of the fibula.

of the retention of function by neoplastic osteoblasts is afforded by the high alkaline phosphatase content of osteosarcomatous tissue, the great increase in the amount of this phosphatase in the sera of patients with osteogenic sarcoma its fall following removal of the tumour, and its further rise with the development of recurrent growth or metastases (Franseen and McLean)

(5) Metastasis

The major risk of osteosarcoma is early metastasis to the lungs. Pulmonary metastases eventually develop in a high proportion—at least three quarters—of all cases. Radiographic evidence of these should be sought in all cases prior to treatment of the primary growth, and again at intervals following amputation. In the majority of cases metastases appear within 2 years from the onset, but they may do so after much longer intervals e.g. 13 years in one of Badgley and Batts's cases. Speed reported a remarkable case in which in spite of clear radiographic evidence of pulmonary metastases, the patient remained alive and well after 13 years the shadows of the metastases having remained almost unchanged, without any treatment, for about 10 years.

Blood borne metastases sometimes appear in parts other than the lungs, e.g. in the skin (Sequeira and Turnbull, Finnerud, Brunschwig and Harmon), in other bones (references in my 1934 work) in the liver or brain (Harding and Courville). Metastases in lymph glands are unusual (references in my 1934 work, Brunschwig and Harmon, 1933 Case I, Warren and Meyer).

OSTEOCLASTOMA

(Giant cell Tumour of Bone)

(1) Histogenesis and nomenclature

The changing views regarding the nature of this tumour have resulted in a diverse and confusing terminology—"myeloma", "myeloid sarcoma", "tumeur a myeloplaxes", "benign giant cell tumour", "osteoclastoma", and "chronic (non suppurative) hemorrhagic osteomyelitis", being only some of the names applied to it. Myeloma and myeloid should be discarded for the tumours are unrelated to the haemopoietic tumours of bone marrow and in particular are quite distinct from the lesions of myelomatosis. Nelaton's "tumeur a myeloplaxes" was erroneous: the tumour giant cells are certainly not megakaryocytes. "Giant cell tumour" is a satisfactory non committal name as long as it is not allowed to lead to confusion of this tumour with giant celled osteosarcomas, and as long as it is not preceded by "benign". Barrie's concept of "chronic hemorrhagic osteomyelitis" is deservedly moribund, its falsity was promptly exposed—too leniently I think—by M. J. Stewart (1922), and such a flimsy piece of speculation should never have been advanced nor taken seriously.

The view that the tumour is an osteoclastoma was suggested in 1922 by Stewart and later adopted by most British pathologists. I find myself, after an initial period of doubt regarding the validity of this view, to convert to it. The close structural similarity of the tumour giant cells with the larger osteoclasts in bone resorptive lesions, the identical appearance of the tumour tissue and of the intra cystic masses of mingled fibroblastic and osteoclastic tissue in

few cases in which trauma is claimed as causative the sequence of events shows that the tumour must have been already well established at the time of the injury. These facts together make it clear that trauma either plays no part at all or only a very infrequent one, in the causation of bone tumours. We will continue to be struck by occasional remarkable coincidences and courts will continue to allow compensation claims for allegedly traumatic sarcomas of bone, but the only attitude for scientific pathologists is one of stringent scepticism.

(c) *Osteitis deformans*

This disease unquestionably predisposes to osteogenic sarcoma. Most osteogenic sarcomas arising after the age of 50 years are in people with Paget's disease. Paget himself was the first to record cases of this association and many subsequent examples have been reported. Indeed cases of this kind are far from uncommon: most surgeons, radiologists and pathologists are familiar with them. The exact proportion of cases of Paget's disease to develop sarcoma cannot be clearly estimated because mild degrees of the former disease are much commoner than gross readily diagnosed lesions. The risk of sarcoma in Paget's disease is certainly less than suggested by Paget's own series in which 3 of 5 patients had sarcoma. Perhaps 5 or 10 per cent of patients with easily detectable clinical or radiographic signs of osteitis deformans may be expected to develop sarcoma. Most of the tumours are clearly osteogenic but a few of them appear fibrosarcomatous or cartilaginous. They arise most frequently in the long bones of the limbs especially the femur, humerus and tibia, but occur also in the scapula, clavicle, pelvis or other bones. A prevalent view that they never arise in the skull is erroneous. Kirschbaum described such a case and referred to 8 others. Albertini made the interesting observation that the sarcomatous change took place multifocally or diffusely in fibrous areas of the affected bones.

(4) Structure and growth

I propose to say nothing of the gross and little of the microscopic structure of these tumours. They have been fully described and depicted in many pathological, surgical and radiological treatises and papers. Suffice it to say that their micro-structure ranges from that of fully differentiated compact bone to anaplastic spindle-celled or pleomorphic-celled growth devoid of recognizable osteoblastic differentiation and that a single tumour sometimes shows a wide range of differentiation. Cellular anaplastic tumours often show patchy differentiation of uncalcified disorderly osteoid tissue which permits their histological recognition (see Figs 302 and 332-334). Great cellular pleomorphism with mixtures of spindle cells and giant cells containing a few or many nuclei is a frequent feature. Sometimes the giant cells resemble those of the osteoclastomas and it is tempting to suppose them to be neoplastic osteoclasts. But proof of this is difficult because multinucleated giant cells are found in many kinds of anaplastic tumours. In Case III below however the tumour contained many typical osteoclasts.

The osteoblastic nature of the sarcoma cells is clearly displayed in cases in which metastatic growths show osteoid or bony differentiation. In 1934 I referred to many records of such metastases and additional examples were reported by Brunschwig and Harmon (1933) and Harding and Courville (1934). Evidence

commonest sites, in order, are—distal end of femur, proximal end of tibia, distal end of radius, proximal end of humerus, distal end of ulna and proximal end of fibula. The remaining 25 per cent of the tumours affect the bones of the head and trunk, especially the pelvis and vertebrae. Lord and Stewart (1943) give references to the rather rare records of osteoclastomas of the skull. It has been stated that giant cell tumour frequently starts in or predominantly involves an epiphysis, and it has even been suggested that it should be called "epiphyseal giant cell tumour". This idea has arisen because of the striking predilection of these growths for the extremities of the long bones, but in the strict sense it is not correct. An osteoclastoma in a young bone with a still unfused epiphysis is situated, not in the epiphysis, but in the metaphysis, and the epiphyseal line is intact, as in the cases in children reported by Stewart and by Burland and Harries.

(3) Structure

(a) *Naked eye appearance*

This varies greatly. Young healthy tumours are uniformly red, brown or sometimes grey or even white, soft and friable. Older tumours become variegated by areas of fibrosis, cysts, haemorrhages, pigmentation, yellow necrosis, or calcification. Early expansion of the bone is usually fairly uniform in all directions, but it may later become irregular and eccentric. A prevalent impression that the radiographic appearances of osteoclastomas, especially the multilocular or "soap-bubble" appearances, are distinctive and "typical" is erroneous, the same appearances can be produced by other expanding non osteogenic tumours.

(b) *Microscopical structure*

The micro structure of healthy parts of the growths, unaltered by secondary changes, is characteristic. The admixture of spindle cells and multinucleated giant cells, the latter often distributed rather uniformly throughout the tissue, is unlike that of any other bone tumour. The giant cells measure 50 to 100 μ or more in diameter, have processes which appear to anastomose with those of the spindle cells, and possess as many as 20 or 40 nuclei each in a single section. These nuclei are identical in appearance with those of the spindle cells, and there are appearances of the fusion of the latter to form the giant cells, appearances interpreted however by some writers (e.g. Burland and Harries) as a fissuring of the giant cells to form spindle cells. Mitotic figures may be found in small numbers in the spindle cells, but are rarely, if ever, found in the giant cells. The vascularity varies greatly, the vascular channels are thin walled and the tumour cells abut closely on them. Except where secondary fibrosis has occurred, collagen fibres are sparse, and there is no good reason for dubbing the spindle cells 'fibroblasts'. Occasionally, lipid laden foam cells are plentiful in parts of the growth.

(4) Behaviour

In the great majority of cases of osteoclastoma with more or less characteristic clinical and histological findings, the tumours pursue a benign course, i.e. they grow slowly, do not transgress the periosteum, do not metastasize and are curable by adequate local removal. As Stewart insisted however incomplete removal of a genuine osteoclastoma, especially by curettage, is followed by recurrence, and some tumours do transgress the bone cortex and periosteum and invade surrounding muscles and other tissues. Lord and Stewart described an

hyperparathyroidism (these masses are often called osteoclastomas, for this very reason) and the conspicuous bone resorptive effect of the tumours, together constitute conclusive evidence that these growths are indeed osteoclastomas.

Those who, like Jaffe *et al* (1940) object to this view and prefer the histogenetically neutral name 'giant cell tumour' do so for three reasons. First, they can scarcely conceive of a genuine neoplasm in which skeletal phagocytes are an essential element—to which it may be replied that phagocytes are not exempt from tumour formation and that in any case osteoclasts are not phagocytes. Secondly they say 'the giant cells of the giant cell tumor while resembling, also show definite differences from indubitable osteoclasts'—to which I reply that on the contrary the resemblance is so close as strongly to suggest their identity. Thirdly it is contended that the spindle cells of the tumours are the essential tumour cells and the giant cells are only fused aggregates of these,—the reply to which is that this does not exclude their osteoclastic nature for normal osteoclasts are formed by syncytial fusion of fusiform and stellate mononucleated cells (see Dawson and Struthers's excellent account 1923). The precise origin of these mononucleated cells—whether from fibroblasts, vascular endothelium or osteoblasts—is beside the point. From what we know of the normal development of osteoclasts we would expect a tumour of osteoclasts to show a mixture of unfused pre-osteoclasts and more differentiated multinucleated syncytia, and this is just what our osteoclastoma shows.

In my opinion then there is little doubt that the giant cell tumour of bone arises from and consists of bone formative (as opposed to marrow) cells which possess the attributes of osteoclasts. I say bone formative cells deliberately because it is neither necessary to assume nor likely that osteoclasts are an immutable self-perpetuating species of cell. As already pointed out it is much more probable that osteoblasts and osteoclasts are merely reversed functional phases of cells of the one kind which we can conveniently call bone formative cells. An osteoclastoma is a tumour of these cells in which the functional bias is osteoclastic rather than osteoblastic.

(2) Age, sex and site incidence

(a) Age

Most large series e.g. Christensen's, show that more than two thirds of the tumours develop between the ages of 10 and 30 years the greatest number of cases being in the third decade. Young children and the elderly are rarely affected. Is it only a coincidence that the pale osteoclastomas reported by Stewart (1922) and Burland and Harries (1924) were both in children?

(b) Sex

Males and females are about equally affected e.g. 170 to 192 in Christensen's series.

(c) Site

As Christensen's figures show about three quarters of the tumours are in the limb bones—about one half of them in the lower and one quarter of them in the upper limbs—and with rare exceptions they are at the ends of the bones. The

shows, I think that osteoclastomas are not invariably benign, that some of them, not initially distinguishable from their benign fellows, invade and metastasize, and that this malignant behaviour does not presuppose supervening sarcoma in a benign tumour, but is a property of certain members of the class *ab initio*

(5) The chondromatous giant-cell tumour

Codman described 9 cases of "chondromatous giant cell tumor" of the upper end of the humerus, and regarded these as a variant of the ordinary giant cell tumour. Jaffe and Lichtenstein (1942) disputed this interpretation and held the growth to be a special form of "benign chondroblastoma" in which groups of multinucleated giant cells are incidentally found. However, the tumour in the following case supports Codman's views

*Case II—(Mr E W T Morris's case)—History—*A male Sudanese aged 25 had noticed gradually increasing swelling of lower end of right tibia for several years. X-ray appearances were those of giant cell tumour. The excised part of the tibia contained a tumour 8 centimetres in diameter distending and replacing the bone and consisting of firm cartilaginous tissue. *Histology* (Fig 329)—Giant-cell and spindle cell tissue is mingled with a cartilaginous matrix. The tumour is simultaneously an osteoclastoma and a chondroma. Its cartilage cells are the same cells as the osteoclastoma cells for everywhere there are gentle transitional forms between typical cartilage and areas of typical giant cell tumour. (Dr H A Sissons is making a thorough study of this specimen.)

The structure of the tumour, which is very different from that of Jaffe and Lichtenstein's "benign chondroblastoma", favours the view of Dawson, Innes and Harvey that the giant cell tumour probably takes origin from a pluripotential cell with capacities for differentiation other than into osteoclasts, or alternatively, that proliferating osteoclasts and chondroblasts can undergo mutual metaplastic transformation.

(6) Lesions simulating osteoclastoma

Masses of tissue with a structure closely resembling that of osteoclastoma, and often designated as such, are found in the bones in generalized osteitis fibrosa (hyperparathyroidism) and also in some of the lesions of localized osteitis fibrosa. These masses are not true tumours, and should not be called such, even when they attain large sizes as in Mathers and Cappell's case, they have no powers of independent progressive growth but retrogress when the bone reforms. Dawson and Struthers did much to correct the mistaken identification of giant celled areas in local or generalized osteitis fibrosa as "myeloid sarcomas" and the correlated mistake of supposing giant cell tumours to be manifestations of localized osteitis fibrosa. They pointed out that the one represents a limited response of the tissues to the requirements of bone resorption, while the other is a progressively growing neoplasm. The close structural resemblance of the two tissues—neoplastic and non neoplastic—is no more surprising than the close resemblance of some chondromas to normal cartilage or of some areas of osteosarcomas to the osteoid tissue of healing callus. At the same time, the very fact that giant-cell tumour tissue can perfectly resemble reactionary osteoclastic tissue is itself good evidence that the former is indeed osteoclastoma.

osteoclastoma of the temporal bone which projected as polypi into the external ear, invaded the transverse sinus and directly infiltrated the cerebellum. There are now many reports of otherwise typical giant cell tumours which have metastasized to lymph glands, lungs or other parts (references by Willis 1934 also Korchow and Jaffe *et al*). King and Jaffe *et al* have attempted to correlate the degree of cellular atypism in individual tumours with their prognosis.

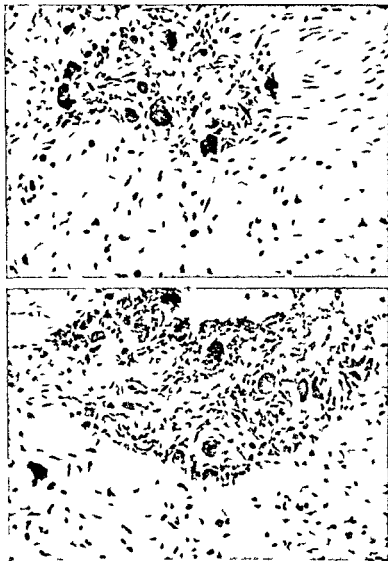


FIG. 329—Case II. Chondromatous osteoclastoma ($\times 150$)

Several writers have suggested that when a giant cell tumour runs a malignant course this is due to supervention of sarcomatous change in a formerly benign tumour, and have pointed to the usually anaplastic structure of the metastases in these cases. But of course the phenomenon of increased anaplasia with metastasis is well known in many kinds of tumours, and in some of the metastasizing osteoclastomas, e.g. those of Finch and Gleave and of Dyke, the structure of the metastases did not depart far from the benign type. The evidence

both myeloid and fibrous, are not tumours but granulomas, they are non invasive, often do not recur even after incomplete removal, and sometimes retrogress spontaneously. Rarely, true tumours—osteoclastomas or fibrosarcomas—may arise from the jaw or its periosteum but these should be distinguished from the ordinary non neoplastic epulides.

The giant celled tumours of synovial tissues, discussed in the next chapter, also should not be confused with osteoclastomas.

RETICULUM CELL SARCOMA OF BONE

Under this title, Parker and Jackson (1939) segregated a group of 17 non osteogenic tumours of bones, which had earlier been diagnosed variously as Ewing's sarcoma, Hodgkin's disease, lymphosarcoma, etc. The tumours affected males and females about equally, occurred chiefly in the second, third and fourth decades, but also in older age groups and were situated most frequently in the femur, clavicle, tibia and humerus. They formed large painful destructive growths, sometimes producing pathological fracture, and devoid of distinctive radiographic appearance, and they gave a variable response to radiation, some responding well but recurring, others not responding at all. Microscopically they consisted of rather pleomorphic rounded or polyhedral cells larger than lymphocytes, with some reticulum fibres between the cells. Although no necropsies had been performed, it was unlikely that these growths were metastatic, since they pursued a relatively benign course and 7 of the 17 patients were well 10 years or more after amputation. Confirmatory reports have been published by other workers, e.g. by Szutu and Hsieh (1942).

In spite of the paucity of necropsy studies there are good grounds for accepting the existence of a non osteogenic sarcoma of bone with rather distinctive characters. There is no doubt that in the past radio sensitive members of this group of tumours have often been called 'Ewing's sarcoma'. But, as Parker and Jackson pointed out, the reticulum cell sarcomas should be distinguished from 'Ewing's tumours' for their age incidence, massive bone destruction, relatively good prognosis and variable response to radiation, are unlike the original Ewing syndrome, and their histology also differs from that of 'Ewing's tumours' as usually described.

Needless to say great care should be exercised in making a diagnosis of reticulum cell sarcoma of bone. There is risk that the errors committed in the past under the captions "endothelioma" and "Ewing's tumour"—the errors of including diverse kinds of growths, especially metastatic ones—may be repeated under this new title. The micro structure of reticulum cell sarcoma is not pathognomonic, but could be simulated by anaplastic carcinoma, lymphosarcoma and other tumours. Each individual tumour must be weighed on its merits and finally diagnosed as reticulum cell sarcoma only when all the evidence, clinical and pathological, compels this conclusion. It remains to add that the precise histogenesis of the tumour is still *sub judice*, but the name "reticulum cell sarcoma" can be accepted pending further studies of well authenticated growths of this kind.

EWING'S TUMOUR

Too much ink has already been spilt in controversy on this chaotic subject, and I cannot undertake here a detailed critical review of its huge and confusing

Myeloid epulis ' (Figs 330, 331) should not be grouped with the osteoclastoma of bone for again resemblance does not denote identity. In many



FIG 330 —Myeloid epulis ($\times 120$)

epulides the giant celled tissue is clearly only a form of inflammatory granulation tissue containing extravasated blood pigments all transitions between ordinary

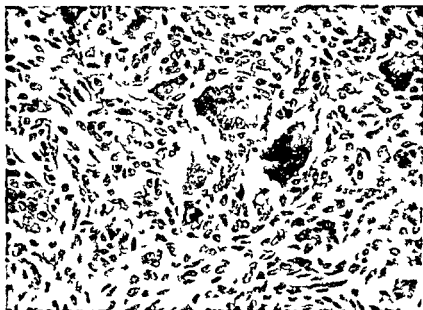


FIG 331 —Myeloid epulis ($\times 300$)

granulation tissue and giant-celled tissue are found. The giant cells are often smaller and less regular than those of osteoclastoma, variable in number and they often contain phagocytosed hemosiderin. With few exceptions epulides

- 8 Huge chondrosarcoma of nasal cavity of cocker-spaniel aged 6, no metastases
- 9 Mixed carcinoma osteosarcoma of thyroid gland of sheepdog aged 10, with osteosarcomatous metastases in lungs (Rudduck and Willis, Case VIII, and see Figs 301, 302, Chapter 36)

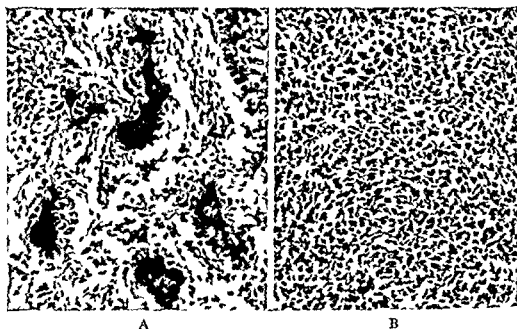


FIG 334—Detail of Fig 333 A = well differentiated bone trabeculae B = undifferentiated part of growth ($\times 120$)

(2) From other animals

- 10 Large chondrosarcoma of upper half of humerus of cat aged 16, with metastases in lungs
- 11 Chondrosarcoma of ribs of a sheep, with metastases in lungs

REFERENCES

- Albertini, A (1928) *Virchows Arch*, 268 259
 Badgley C E and Batts M (1941) *Arch Surg* 43 541
 Bennett G E and Berkheimer G A (1941) *Surgery* 10 781
 Bland Sutton J (1922) *Tumours Innocent and Malignant* Chapters IV VII London
 Brunschwig A and Harmon P H (1933 and 1935) *Surg Gyn Obst*, 1933, 57 711 and 1935 60 30
 Burland T H and Harnes D J (1924) *Brit J Surg* 12 254
 Chorobski J Jarzynski J, and Ferens E (1939) *Surg Gyn Obst*, 68 677
 Christensen F C (1925) *Ann Surg* 81 1074
 Codman E A (1931) *Surg Gyn Obst* 52 543
 Cole W H (1926) *Surg Gyn Obst* 42 359
 Colville H C and Willis R A (1933) *Amer J Path* 9 421
 Cosin L (1935) *Brit J Surg* 23 110
 Cruickshank A H (1945) *J Path Bact* 57, 144
 Dawson E K, Innes J R M and Harvey W F (1938) *Edinb Med J*, 45 491
 Dawson J W and Struthers J W (1923) *Edinb Med J* 30 421

literature To some extent this has already been done in previous papers (Colville and Willis 1933 Willis 1938 and 1940) I have read also many accounts of 'Ewing's tumours' other than those there reviewed including those of Rix and Geschickter, Geschickter and Maseritz Potozky and Freid, Foot and Anderson Gharpure and Lichtenstein and Jaffe (1947) The following are my conclusions

- (1) Ewing's tumour is not a pathological entity it is merely a (rather ill defined) syndrome of a non osteogenic round celled, radio sensitive tumour in a bone usually a long bone usually in a young subject and usually causing diffuse elevation of the periosteum This syndrome can be caused by several different kinds of tumours
- (2) In the majority of cases heretofore diagnosed as Ewing's tumour the tumours have been metastatic
- (3) So called Ewing's tumours in children and adolescents are usually metastatic neuroblastomas
- (4) Primary reticulum cell sarcoma accounts for a minority of reported Ewing's tumours

The evidence for (2) is given in my earlier papers and in Carl Sternberg's last paper (1935) The evidence for (3) is given in Chapter 55 of this book, and I have also to record that several workers have written to me to say that in recently reviewing their Ewing's tumours they have found some of them to be neuroblastomas It is significant too that Rix and Geschickter head a section of their paper on tumours of the spine— Sympathicoblastoma (and Ewing's sarcoma) and that they conclude 'No typical Ewing's sarcoma of the spine was found in the present series, and the tumors previously classed as such were thought on further study to be sympathicoblastomas' In their paper on 135 Ewing's sarcoma⁶ Geschickter and Maseritz stated 'Neuroblastoma was found to resemble Ewing's sarcoma clinically and microscopically Both tumors respond to irradiation The presence of rosettes and neurocytes are distinctive histological features of neuroblastoma I also believe that neuroblastoma rosettes are distinctive, and in my opinion the rosettes in Ewing's tumours' depicted by F W Stewart Foot and Anderson and Gharpure show these almost certainly to have been neuroblastomas

A radio sensitive reticulum cell sarcoma occurring in a young person might qualify for the Ewing syndrome and there are some workers who like Stout feel unable to separate reticulum cell sarcoma and Ewing's tumor Most workers however, for the reasons given in the preceding section agree that in general reticulum cell sarcomas do not resemble 'Ewing's tumours' as commonly described and that the former should be segregated out of the heterogeneous dumping ground which the latter has become When we have removed from this dumping ground many metastatic neuroblastomas some metastatic lymphosarcomas and other secondary tumours which it has been admitted have been placed there occasional non ossifying osteogenic sarcomas which have also been wrongly cast there and occasional radio sensitive reticulum-cell sarcomas more or less fulfilling the Ewing criteria then there will probably be nothing left in the dump

- Schlotthauer C F (1942) *N Amer Vet*, 23 470
- Sequeira, J H, and Turnbull H M (1914) *Proc Roy Soc Med*, 8, Derm Sect p 8
- Speed K (1943) *Surg Gyn Obst* 76 139
- Speiser F (1925) *Virchows Arch* 258, 126
- Sternberg C (1935) *Frankfurt Z Path* 48 525
- Stewart F W (1933) *Amer J Path* 9 801
- STEWART, M J (1922) The histogenesis of myeloid sarcoma with a criticism of the chronic haemorrhagic osteomyelitis theory *Lancet* ii 1106
- Stewart M J (1922) *Brit J Surg* 10 322
- STOCKS, P, and BARRINGTON, A (1925) "Hereditary disorders of bone development" *Treasury of Human Inheritance* London (A detailed statistical analysis with many pedigrees full reference lists and illustrations)
- Stout A P (1943) *Amer J Roent* 50 334
- Szutu C and Hsieh C (1942) *Ann Surg* 115 280
- Twort C C and Twort J M (1932) *J Path Bact* 35 976
- Warron S (1931) *Amer J Path* 7 161
- Warren S and Meyer R W (1938) *Amer J Path* 14, 605
- Weber O (1866) *Virchows Arch* 35, 501
- Willis R A (1934) *The Spread of Tumours in the Human Body* London
- Willis R A (1938) *Med J Austral* ii 717
- WILLIS, R A (1940) Metastatic neuroblastoma in bone presenting the Ewing syndrome with a discussion of Ewing's sarcoma *Amer J Path*, 16 317
- Wirth J E and Shumkin M B (1943) *Arch Path* 36, 83

- Dyke S C (1931) *J Path Bact* 34 259
- Ernst P (1900) *Beitr path Anat* 28 255
- Feldman W H (1932) *Neoplasms of Domesticated Animals* Chapters VI and VII Philadelphia
- Feldman W H and Ford F A (1932) *Amer J Cancer* 16 377
- Finch E F and Gleave H H (1926) *J Path Bact* 29 399
- Finnerud C W (1924) *Arch Derm Syph* 10 56
- Foot F W and Anderson H R (1941) *Amer J Path* 17 497
- Franssen, C C and McLean R (1935) *Amer J Cancer* 24 299
- Fry H, and Shattock C E (1926) *Brit J Surg* 14 337
- Geschickter C F and Maseritz I H (1939) *J Bone Joint Surg* 21, 26
- Gharpure V V (1941) *Amer J Path* 17 503
- Grout J L A (1945) *Proc Roy Soc Med* 38 345
- Haddow A and Blake I (1933) *J Path Bact* 36 41
- Harding W G and Courville C B (1934) *Amer J Cancer* 21 787
- Hueper W C (1942) *Occupational Tumors* Springfield
- Hunter D and Wiles P (1935) *Brit J Surg* 22 507
- JACOBSON S A (1940) Critique on the inter relationships of the osteogenic tumors
Amer J Cancer 40 375
- JAFFE H L, LICHTENSTEIN L and PORTIS R B (1940) Giant cell tumor of bone
Arch Path 30 993
- JAFFE H L and LICHTENSTEIN L (1942) Benign chondroblastoma of bone *Amer J Path* 18 969
- JAFFE H L, and LICHTENSTEIN L (1943) Solitary benign enchondroma of bone
Arch Surg 46 480
- JAFFE H L (1943) Hereditary multiple exostosis *Arch Path* 36 335
- JAFFE H L (1946) Fibrous dysplasia of bone *Bull N Y Acad Med* 22 588
(Jaffe's and Lichtenstein's papers are valuable outlines and sources of reference)
- Keith A (1920) *J Anat* 54 101
- King E S J (1932) *Brit J Surg* 20 269
- Kirschbaum J D (1943) *Arch Path* 36 74
- Korschow W J (1933) *Z Krebsforsch* 38 380
- Kósa M (1929) *Virchow's Arch* 272 166
- Landois F (1920) *Virchow's Arch* 229 101
- LICHTENSTEIN L and JAFFE H L (1943) Chondrosarcoma of bone *Amer J Path* 19 553 (A valuable account)
- Lichtenstein L and Jaffe H L (1947) *Amer J Path* 23 43
- List C F (1943) *Surg Gyn Obst* 76 480
- Lord O C and Stewart M J (1943) *J Laryng* 58 263
- Martin E K (1925) *Brit J Surg* 13 Suppl p 26
- MARTLAND H S (1931) The occurrence of malignancy in radioactive persons *Amer J Cancer* 15 2435 (An excellent account of these occupational osteogenic sarcomas)
- Mathers R P and Cappell D F (1938) *J Laryng* 53 656
- McCall J W, Dupertuis S M and Gardiner F S (1944) *Laryngoscope* 54 1
- Money R A (1943) *Med J Austral* 1 181
- Muller E (1913) *Beitr path Anat* 57 232
- Orr J W (1931) *J Path Bact* 34 265
- Paget J (1876) *Medico Chir Soc Lond* (New Sydenham Soc Vol 172)
- PARKER I and JACKSON H (1939) Primary reticulum cell sarcoma of bone *Surg, Gyn Obst* 68 45
- Pemister D B (1930) *Surg Gyn Obst* 50 216
- Pich G (1938) *Beitr path Anat* 101 181
- Potozky H and Fraud J R (1939) *Amer J Cancer* 36 1
- Pybus F C and Miller E W (1938) *Brit Med J* 1 1300
- Pybus F C and Miller E W (1938 and 1940) *Amer J Cancer* 1938 33 98 and 1940 40 47 54
- Ratchiffe H L (1940) *Amer J Path* 16 237
- Recklinghausen, F (1885) *Virchow's Arch* 100 503
- Rix R R and Geschickter C F (1938) *Arch Surg* 36 899
- Rudduck H B and Willis R A (1938) *Amer J Cancer* 33 205

BENIGN SYNOVIOMA

(1) Age, sex and site incidence

These not uncommon tumours arise in young and middle aged adults, they rarely appear in children or old people. The multiple form in joints which are the seat of hyperplastic synovitis is more common in men than in women, but the reverse applies to the solitary synoviomas of tendon sheaths.

Solitary tumours are commoner than multiple ones, and arise from tendon sheaths much more often than from joints or bursae. Multiple tumours are much commoner in large joints than in tendon sheaths, the knee joint is by far the most commonly affected joint. The commonest sites of solitary synoviomas of tendon sheaths are in the hands, especially the fingers, the feet are less often affected and other sites are rare. The flexor tendon sheaths are affected much more often than the extensor. The tumours grow outward from the sheath and rarely project into its cavity or involve the tendon. The right hand is affected more frequently than the left, a difference which has been held to indicate trauma as a causative factor.

(2) Neoplasm or granuloma?

The view that the "xanthomas" and giant cell growths of synovial membranes are not true tumours but inflammatory granulomas was advanced in 1913 by Fleissig and has recently (1941) been strongly upheld by Jaffe, Lichtenstein and Sutro, who summarize this opinion in the title "pigmented villonodular synovitis". There is no doubt that the widespread brown seaweed-like synovial growths sometimes found filling a large joint are inflammatory and not neoplastic, and that these often include small or large nodules closely resembling in structure the solitary giant cell growths which are usually regarded as tumours. On the other hand, from the general structure, cellularity and mitotic activity of many of the solitary growths it seems clear that they are indeed neoplasms. Many of these have the structure of more or less cellular fibromas, with few or no giant cells and foam cells and little or no pigment, and many of them appear to be isolated growths from synovial membranes devoid of any signs of generalized villous synovitis.

However, this seeming contradiction is not as serious as it appears. We know of many other organs in which hyperplasia passes insensibly into neoplasia and where hyperplastic and neoplastic lesions may closely resemble one another and may be difficult to separate on purely microscopical grounds, e.g. the breast, uterus, liver, thyroid and other ductless glands. In these organs also, neoplasia supervening on hyperplasia is often multicentric. The concept is quite admissible then, that many of the larger nodular masses which develop in a villous synovitis are indeed multiple tumours similar to those that often develop singly in membranes devoid of previous hyperplastic changes. The presence of haemosiderin and lipid laden phagocytes in some of the solitary tumours is not surprising, for, since hyperplastic masses of synovial tissue are apt to display these secondary changes, neoplastic masses of the same tissue might be expected to display similar changes.

A prevalent view that the multinucleated cells in synoviomas are merely foreign body giant cells calls for correction. True foreign body giant cells may

CHAPTER 44

TUMOURS OF SYNOVIAL TISSUES

INTRODUCTION

Two rather distinct groups of synovial tumours are recognizable

- (a) Moderately common benign predominantly fibroblastic and giant celled growths, most often arising from tendon sheaths and variously designated fibroma endothelioma giant cell tumour myeloid tumour, myeloma xanthoma, benign synovioma or teno synovioma
- (b) Rare malignant growths either of predominantly cystic papillary structure with the synovia filled spaces lined by epithelium like cells in single or multiple layers or diffusely spindle-celled or pleomorphic celled or often showing both types of structure usually arising from the capsules of large joints or from bursae in their neighbourhood and designated malignant synovioma synovial sarcoma or 'sarco mesothelioma'

While most tumours fall readily into one or the other of the two groups, distinction is not absolute some benign tumours (e.g. those described by Black, 1936 and 1940) contain plentiful synovial mucin and spaces lined by epithelium like cells resembling those seen in the malignant group and some of the diffusely cellular sarcomas are clearly the malignant counterparts of the common benign fibromatous and giant celled growths (see King 1931)

Interpretation of the structure of synovial tumours necessitates clear concepts regarding the structure of normal and hyperplastic synovial membranes. The once prevalent view that the cells lining synovial cavities form a continuous pavement endothelium distinct from the underlying connective tissue was erroneous. The synovial surface is a specialized free connective tissue surface the cells of which are modified connective tissue cells. Modern histologists speak of the lining cells as fibroblasts (Maximow and Bloom 1944 Bremer and Weatherford 1944). In some places especially in hyperplastic lesions the lining cells are plump and closely aggregated into a pseudo epithelial layer in other places they are sparse and flattened. The cells on the surface and those just beneath it are not different types of cells, but variants of one type—the synovial fibroblast and between this and the ordinary collagen producing fibroblast of the surrounding tissue no sharp line of separation can be drawn. Further at chondro synovial junctions there are transitions from cartilage to synovial tissue. That synovial cells are only modified fibroblasts is shown also by the transformation of the latter into the former under appropriate conditions, as in false bursae and joints. The close kinship of articular fibrous synovial and cartilaginous tissues explains the structural variations in the tumours of synovial tissues their varying mixtures of synoviomatous and fibromatous features their angiomatoid characters, and their occasional formation of cartilage or bone as depicted by Buxton

great histogenetic significance. Hence the name "xanthoma" is to be deprecated, for it focuses attention on a purely incidental feature and causes confusion with the lesions of "xanthomatosis" and other phagocytic granulomas to which synoviomias are unrelated. For various reasons, other names are also inappropriate. "Endothelioma" is inappropriate for reasons already given. "Giant-cell tumour" is unsatisfactory, since some tumours contain few or no giant cells. "Myeloid tumour" and "myeloma" are particularly objectionable, for the tumours are quite unrelated to those of bone marrow and bone, and indeed their structure does *not* resemble that of the giant cell tumour (osteoclastoma) of bone.

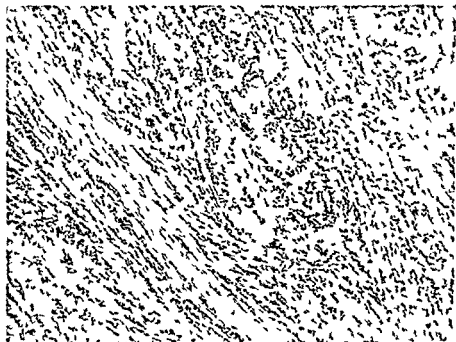


FIG. 336.—From a suprapatellar synovioma 3.5 centimetres in diameter from a man of 21 showing lines and clumps of polyhedral and fusiform tumour cells and densely collagenous partly hyaline matrix ($\times 100$).

For this reason, as well as for others mentioned by Jaffe *et al*, Geschickter and Copeland's suggestion, that giant cell tumours of tendon sheaths are osteoclastomas of sesamoid bones, is absurd.

(4) Growth and behaviour

With rare exceptions, the predominantly fibromatous or giant celled tumours of tendon sheaths and other synovial tissues are slowly-growing non invasive *benign tumours, readily cured by simple enucleation*. At the time of their removal on account of pain or mechanical disability, they have seldom attained diameters of more than 2 or 3 centimetres, but tumours of 5 centimetres or more are recorded. There is usually no difficulty in distinguishing clinically between the common slowly growing circumscribed benign synoviomias and the rare, rapidly growing invasive synovial sarcomas. Professor M. J. Stewart has shown me a specimen of undoubtedly malignant synovioma of giant celled type, which invaded neighbouring soft tissues.

possibly occur in some of the tumours in which lipid phagocytes abound but as Stewart and Flint insisted, most of the giant cells are undoubtedly tumour cells. Their nuclei which are identical in appearance with those of the surrounding mononucleated tumour cells are scattered throughout their cytoplasm. They rarely contain lipoids but they often contain haemosiderin. These large cells have all the appearance of being syncytial aggregates of the smaller tumour cells and not primarily phagocytic at all. Since however, the tumour cells are of mesenchymal type it is not surprising that they themselves should take up extravasated pigments. The haemosiderosis of the cells does not mean that they are merely scavengers.



FIG. 335.—From a mainly fibromatous synovioma 2 centimetres in diameter attached to flexor tendon sheath of thumb of a man of 33 years showing synovial clefts with villous projections in the tumour ($\times 100$)

(3) Structure, histogenesis and nomenclature

The tumours arise from and consist of synovial tissue and are therefore appropriately named synoviomas. Sub-division of the group into fibrous mucinous vascular giant-celled cartilaginous osseous lipomatous and mixed types is unnecessary and impracticable for many tumours are mixed showing combinations of the different structural variants. The commonest of these are

1. *cellular and fibrous* which are often seen in combination and in which

2. *cellular clefts* are often present (see Figs 335 336). The tumours

3. *cellular clefts* in which polyhedral spindle shaped or

4. *cellular clefts* as matrix these areas often alternate

5. *cellular clefts* areas. Primarily, many of the solitary

6. *cellular clefts* little or no extravasated blood pigment or

7. *cellular clefts* substances and the phagocytic activity

8. *cellular clefts* prominent are secondary and of no

Case I—History—For 18 months a man of 71 had an enlarging mass on the inner aspect of his knee joint. Operation showed this to be a well defined hemispherical tumour 14 centimetres in diameter attached to the external surface of the capsule of the joint by a pedicle 4 centimetres in diameter. A disc of the capsule was removed along with the tumour which weighed 540 grammes. On section it was found to consist of a fine honeycomb of spaces filled by mucinous material. *Microscopically* (Fig 338) these were lined by layers of cells of variable appearance and thickness in some places resembling an epithelial reticulum in others consisting of strands of elongated cells traversing mucinous material, and in others resembling myxoma.

(1) Age, sex and site incidence

Knox's and Fisher's reviews show that malignant tumours of synovial membranes occur with about equal frequency in men and women. They may



FIG 338—*Case I* Malignant synovioma of pseudo-epithelial type showing a tumour meshwork with mucus filled spaces ($\times 120$)

appear at any age after childhood, the greatest numbers of patients being in the third and fourth decades. In about one half of the cases the growths arise in the region of the knee either from the capsule of the knee-joint itself or from neighbouring bursae, especially on the popliteal aspect. The other principal sites of origin are the ankle region and foot, forearm wrist, elbow and thigh. Very few of the tumours have commenced in the hands (the commonest site of benign synoviomias) toes, shoulder girdle, or in the joints of the head, neck and trunk. Most of the tumours arising from joint capsules project externally from the capsule and often do not invade the joint cavity. This suggests that their origin is less often from the lining of the joint itself than from synovial cysts in the capsule—a suggestion strengthened by the predilection of the tumours for the capsule of the knee joint, where such cysts are common. However, there is no evidence that the common synovial ganglia of the wrist region are predisposed to tumour formation.

MALIGNANT SYNOVIOMAS OR SYNOVIAL SARCOMAS

Malignant tumours of synovial origin are either (a) solid anaplastic spindle celled or pleomorphic celled sarcomas in which synovial differentiation is lacking or indefinite or (b) cystic or papillary growths of pseudo epithelial structure often containing gelatinous synovial secretion. These two types are probably



FIG. 337.—Malignant tenosynovioma of foot of pseudo-epithelial type. A = papillary structure. B = pseudo-acinar structure. ($\times 150$)

not distinct but represent merely the more or less anaplastic tumours of the one kind. Those of type (a) exemplified by my necropsy Case No. 218 (Willis 1934) are rarer than those of type (b). Good accounts include those of Prym, Knox, Hutchison and Kling, Briggs and Fisher. I have examined two specimens of the cystic mucinous type of growth, one of these depicted in Fig. 337 arose in the sheath of one of the flexor tendons of the foot in a man of 51 years and the following are brief notes of the other:

CHAPTER 45

ANGIOMAS TUMOURS AND TUMOUR-LIKE OVERGROWTHS OF VASCULAR TISSUE

INTRODUCTION

SEVERAL factors complicate the discussion of tumours of blood vessels and lymph vessels. In the first place, most so called 'angiomas' are not true tumours but vascular malformations or 'hamartomas', while some others are vascular masses of reparative tissue. But, in the second place, distinction between the true neoplasms and the hamartomas of vascular tissue is not always easy, for in the latter seemingly infiltrative structure and multicentric formation may readily simulate invasive growth and metastasis. Thirdly, many malignant tumours of other kinds have been wrongly identified as angiomatous merely because of their great vascularity. Fourthly, since the potencies of proliferating mesenchymal tissues are very diverse, sharp separation of angiomas from other mesenchymal growths is to some extent arbitrary. Before going on to consider angiomas as neoplasms, let us consider these four confusing factors more fully.

(1) Most "angiomas" not true tumours

Most pathologists will concur in this proposition. Briefly, the grounds for it are as follow:

(a) Many "angiomas" are congenital. Those of the skin, which are the commonest form of 'birthmarks', are obvious at birth or are noticed soon afterwards (see Figs 339-343). Fitzwilliams found that 83 per cent of vascular naevi of the skin were noticed at birth, and an additional 13 per cent within 6 months. Those of the deeper tissues may not be discovered until later in life, but these also, when they involve functionally important parts such as the nervous system, usually give evidence of their presence during childhood or early adulthood. Parkes Weber speaks of naevi as 'developmental—mostly congenital—dysplasias'.

(b) No structural distinction is possible between "angiomas" and acknowledged vascular malformations such as plexiform or serpentine angiomas or mere supernumerary vessels. Indeed the structure of many "angiomas" shows clearly that they are masses of tangled or deformed supernumerary vessels—capillaries, veins, arteries, or all three. The larger vessels often have well developed muscle coats or irregular masses of muscle fibres in their walls (see Fig 340, and Case I below).

(c) Above all, the common vascular hamartomas have no powers of progressive disproportionate growth. Like any other malformation, the birthmark grows along with the tissues of which it is a blemish, then, unless accidents occur in it it usually ceases to increase. Accidents which may cause its enlargement, namely, haemorrhages, cystic changes, inflammation, thrombosis and oedema, may give it a false clinical appearance of neoplastic growth, and in certain situations,

(2) Structure

The two main varieties of structure found alone or together, in synovial sarcomas are

(a) Cystic and papillary formations with synovial fluid in the spaces

The spaces are often lined by a compact layer of polyhedral tumour cells one or several layers thick giving a pseudo epithelial appearance superficially resembling that of disorderly papillary adenocarcinoma (Figs 337-338). Closer examination however usually reveals the non-epithelial character of the cell layers: these possess no proper basal border, but merge with the diffusely arranged surrounding cells. The relative amounts of pseudo-epithelium and intervening diffusely cellular tissue vary widely: sometimes as in the specimen of Fig. 338 the bulk of the tissue forms pseudo carcinomatous structures, in other tumours the bulk is diffusely sarcomatous with only occasional clefts lined by compact cell layers.

(b) Diffusely cellular sarcoma

This consists of either spindle cells, polyhedral cells or pleomorphic cells. Indefinite epithelium like clumps may be found in parts and myxomatous areas also occur.

(3) Behaviour

Only occasional tumours of this kind appear to have been cured by excision or amputation. In most cases recurrence or metastasis has developed. The lungs are the main site of metastases and these may appear several years after removal of the primary growth: e.g. 4 years in Knox's third case. Metastases in the regional lymph glands as in my necropsy case referred to above are unusual. In structure the metastases may reproduce the distinctive synovial characters of the primary growth as in Fisher's first case or they may be more anaplastic, as in my case.

REFERENCES

- Black W. C. (1936) *Amer. J. Cancer* 28: 481.
 Black W. C. (1940) *Ibid.* 39: 199.
 Bremer J. L. and Weatherford H. L. (1944) *Text book of Histology* p. 146. Philadelphia.
 Briggs C. D. (1942) *Ann. Surg.* 115: 413.
 Buxton St. J. D. (1923) *Brit. J. Surg.* 10: 469.
 FISHER H. R. (1942) Synovial sarco-mesothelioma. *Amer. J. Path.* 18: 529. (A useful review of the pseudo-epithelial tumours).
 Hutchison C. W. and Kling D. H. (1940) *Amer. J. Cancer* 40: 78.
 JAFFE H. L., LICHTENSTEIN L. and SUTRO C. J. (1941) Pigmented villonodular synovitis, bursitis and tenosynovitis. *Arch. Path.* 31: 731.
 KINC F. S. J. (1931) Concerning the pathology of tumours of tendon sheaths. *Brit. J. Surg.* 18: 594. (A useful review).
 Knox L. C. (1936) *Amer. J. Cancer* 28: 461.
 Maximow A. A. and Bloom W. (1944) *Text-book of Histology* p. 154. Philadelphia.
 Prym P. (1931) *Virchows Arch.*, 279: 71.
 Stewart M. J. and Flint E. R. (1915) *Brit. J. Surg.* 3: 90.
 Willis, R. A. (1934) *The Spread of Tumours in the Human Body* p. 437. London.

an already existing malformation Thrombosis, organization and fibrosis some times lead to reduction in size of "angiomas"

(d) Some acquired 'angiomas' are not malformations but masses of vascular reparative tissue or ectatic vessels Thus, Mailer advanced good reasons for believing that some of the so called "angiomas" of skeletal muscle are post traumatic masses of granulation tissue under peculiar mechanical conditions, and there is little doubt that not a few of the acquired "angiomas" of skin and mucous membranes are merely masses of inflammatory tissue—*inflammatory granulomas*—the products of delayed or thwarted healing Many acquired telangiectases, such as those of the face of plethoric elderly people, are of course due merely to local dilatation of vessels from obstructive or degenerative causes

Before assuming, then, that any given mass of highly vascular tissue is a truly neoplastic angioma, the question should be asked can this be either a vascular malformation, altered maybe by supervening accidental changes, or an extravagant mass of post-traumatic or post-inflammatory reparative tissue, or merely a varicosity or ectasia? The answer will usually be in the affirmative

(2) Distinction between vascular hamartomas and neoplasms sometimes difficult

Vascular hamartomas, by their very nature, are usually poorly demarcated and show intimate mingling of the superfluous vessels with the normal tissues of the part This may give a false appearance of invasive infiltration, and, especially if the hamartoma consists of fine capillary vessels or of more cellular areas of non canalized vasoformative tissue, its microscopical appearance may closely simulate that of an invasive growth If also, as is not uncommon multiple hamartomas of this kind are present in several tissues, say in the spleen and liver or in the liver and lungs then these multiple foci may simulate metastases In 1934 I reviewed and discussed many examples of this kind to which may be added the case described by Taylor and Moore While in many of these cases especially in infants, it is clear that multicentric growth accounts better for the findings than metastasis, in some others in adults it is difficult to reach a confident decision, and the possibility of the growths being metastasizing angio sarcomas must be admitted (*see below*)

(3) Vascular tumours of other kinds wrongly diagnosed as "angiomas"

No modern pathologist should be so misled by finding blood within adeno carcinomatous spaces that he mistakes renal or other carcinomas for "haemangio endotheliomas", as was once done Yet as Stout properly points out, the last edition of Ewing's text-book (1940) contains an illustration (Fig 133) labelled "angio endothelioma of bone" which almost certainly perpetuates this old error, and Thomas (1942) has made a similar mistake

More excusable, but still unfortunate, is the tendency to assume that diffusely cellular highly vascular growths of uncertain nature are angioblastic This assumption has led to many errors of diagnosis Anaplastic growths both carcinomas and sarcomas may contain abundant vessels closely invested by the tumour cells in a way falsely suggesting special angioblastic properties of the tumours The question arises what degree of vascularity, what ratio of vascular channels to haemovascular cellular growth shall we require in an anaplastic mesenchymal tumour in order to identify it as a specifically vasoformative one? I find this

e.g. in the brain, such enlargement may make it as dangerous as any tumour and necessitate its removal. Even when an angioma appears to extend its territory



FIG. 339.—Angioma of dermis of shoulder present since birth excised when child was 12 months old ($\times 120$)



FIG. 340.—Fom a plaque like angioma of skin of shoulder 5 centimetres in diameter excised when child was 14 months old showing a capillary plexus and part of wall of a large arterial vessel ($\times 150$)

without having suffered any such accidents this is probably due, not to proliferative growth but to canalization and establishment of a blood flow in fresh parts of

(1) Haemangiomas of particular tissues

(a) *The skin and subcutis*

The familiar "angiomas" or vascular naevi of the skin—'De Morgan or ruby spots', 'spider naevi', "mulberry naevi", 'port-wine stains', etc.—are adequately described in many text books, have recently been well summarized by Harvey *et al* and by Weber, and call for no special description here. Their structural variants, described as capillary, cavernous and plexiform, are often seen in combination, and the lesion often extends also into the subcutaneous

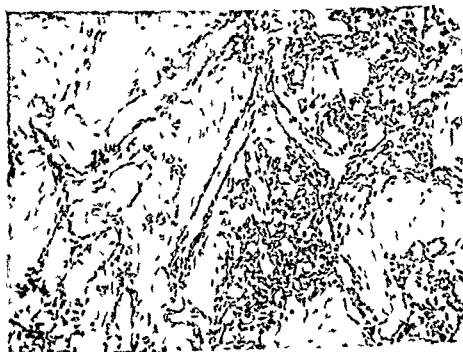


FIG 341.—From a pedunculated birthmark 1 centimetre in diameter, of skin of neck excised from a woman aged 30 showing patent capillary channels and patches of incompletely canalized vasoformative tissue ($\times 150$)

tissues and occasionally into the underlying muscles or bones. A type of structure particularly noteworthy because it may simulate that of a cellular neoplasm, is the poorly canalized, capillary type with tangled masses of closely aggregated vasoformative cells and but few patent vascular channels (Fig 341). Canalization of such tissue probably accounts for the seeming extension of some angiomas. The following case exemplified the great variety of structure seen in angiomas.

Case 1—Male 2. **History—**Birthmark of skin of calf present since birth with no change until recently, when it became painful was excised. It was a cutaneous and subcutaneous angioma 4 centimetres in diameter from which some thrombosed veins passed through the deep fascia into the muscle. **Histology—**Growth was a mixture of vascular channels of great diversity including canalized and non-canalized capillaries, large cavernous spaces, well formed arteries and many large vessels with irregular lumina and thick muscular walls in which bundles of smooth muscle fibres ran in various directions. Many large patches of muscle contained relatively few vascular channels. Many normal cutaneous glands and nerves were submerged in the vascular growth, some of the nerves contained angiomatous vessels (Fig 342).

question difficult to answer. On the one hand I am satisfied that great vascularity has often led to a false diagnosis of malignant angioma and on the other hand I have seen several tumours in which a highly vascular pattern appeared to be a distinctive and widespread feature strongly suggestive of a special angioblastic habit of growth. Reasonable confidence regarding the angiomatous character of such a tumour is however to be attained only by a most thorough examination of all parts of it and in many cases by necropsy study to ensure that the growth in question is indeed primary and not a peculiar metastasis of some unsuspected primary tumour elsewhere.

It is to be recalled here that highly haemorrhagic characters are not peculiar to angiomatous growths but are seen also in chorion epithelioma and in anaplastic carcinomas and sarcomas. Ogilvie and Mackenzie reported two tumours as 'malignant haemangio endotheliomas' and later with commendable frankness retracted this diagnosis in one case and identified the growth as chorion epithelioma.

(4) The diverse potencies of mesenchymal tissues

It was pointed out in Chapter 41 that the ready metaplastic conversion of proliferating mesenchymal tissue of one kind into tissue of another kind seen in both non neoplastic and neoplastic lesions makes the grouping of mesenchymal tumours into separate species somewhat arbitrary. Since fibromas sometimes ossify, chondrify or undergo mucoid change, why should they not sometimes undergo predominant vascular differentiation as they grow? Such a conversion indeed happens with the meningiomas, some of these are so abundantly vascular that they have been called angioblastic meningiomas (Wolf and Cowen, Bailey and Bucy) and all gradations are seen between structurally typical meningiomas and predominantly angiomatoid growths. Evidently then predominantly angiomatoid structure in a mesenchymal tumour does not necessarily denote a specific vascular origin. Every actively growing tissue is bound to have an adequate blood supply and actively growing mesenchymal tumours in particular may well develop their vascular channels to an extravagant degree for their tissue is of the very lineage that makes blood vessels. Let us be cautious then, not to pronounce highly vascular mesenchymal growths 'angiomatous', save on very secure grounds.

A BRIEF SURVEY OF ANGIOMATOID MALFORMATIONS

Because most so called benign angiomas are not neoplasms but malformations, this book is not primarily concerned with them. However some knowledge of their distribution and structure is necessary to a critical consideration of tumours believed to be truly angiomatous. Hence a brief survey of them is given here under the following main heads:

- Haemangiomas of particular tissues
- Multiple haemangiomatous syndromes
- Lymphangiomas



FIG 343—*Case II* Congenital angioma of muscle, showing muscle fibres separated by mesenchymal tissue with many blood vessels B—includes also many leucocytes ($\times 120$)

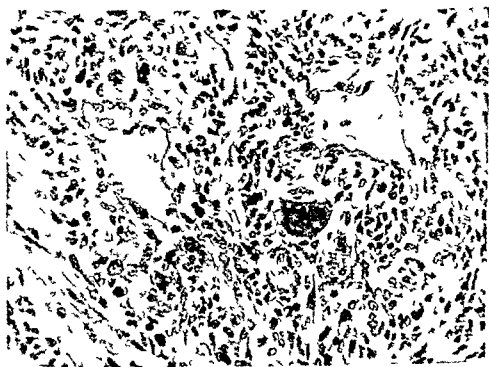


FIG 344—*Case II* Details of vascular spaces intervening mesenchyme and a multinucleated giant cell ($\times 300$)

(b) *Skeletal muscles*

Angiomas of muscles have been described and reviewed by Jenkins and Delaney, Mailer and MacDermott. In over 80 per cent of reported cases the patients have been under 30 years of age many of them children. The muscles most often affected are those of the thigh and calf the biceps and triceps of the arm, latissimus dorsi and masseter. Besides the developmental origin suggested by the age incidence, trauma may produce angiomatoid lesions in muscle as suggested by Mailer, or possibly enlargement of a developmental lesion as the result of injury, haemorrhage and thrombosis may bring it to clinical notice or



FIG. 342.—*Case I*. A nerve bundle surrounded by and containing cavernous vascular channels ($\times 150$)

may simulate neoplastic growth. The following two examples of angiomas of muscles are worthy of note.

Case II—At birth a male infant was noticed to have a bulky swelling of its *rectus femoris*. Exploratory operation disclosed a very vascular growth diffusely involving the distal two-thirds of the muscle. A piece removed for microscopical study showed the bundles of muscle fibres separated by richly vascular mesenchymal tissue including many capillary vessels and small veins, many plump perivascular fusiform and stellate cells, scattered collections of lymphocytes and other leucocytes, and some large irregular multi-nucleated cells resembling megakaryocytes (Figs 343–344). The appearance was thus that of a highly vascular young mesenchymal tissue with some haemopoiesis also in progress.

Case III—For 5 years a woman aged 21 had noticed a rounded mass near the sternum; this was excised and found to be an ill-defined vascular growth 2 centimetres in diameter in the pectoral muscle. *Histology*—Typical benign cavernous angioma mingled with muscle fibres; the walls of the vascular spaces contained plentiful smooth muscle.

sub division clinically convenient, it is not warranted pathologically. With rare and doubtful exceptions, all angiomas of the nervous system are developmental vascular hamartomas, and all gradations between and combinations of the several structural types occur. The variability in structure and distribution of the lesions is well shown in Wolf and Brock's series. The cerebellar growths show as little structural evidence of neoplastic qualities as other "angiomas", attribution of such qualities to them by clinicians has been merely because they are space occupying lesions in a region where any enlargement—from cystic changes or vascular accidents—is certain to cause dangerous results.

Weiss described a cerebral cavernous angioma which contained also bone and glial tissue. Bailey and Ford pointed out that angiomas of the nervous system, like those of other regions, may show sclerosing, pigmentary and lipid changes, and that both neuroglia and connective tissue may participate in the sclerosis. An interesting and frequent feature of angiomas of the brain is the presence in or around them of many small degenerated vessels which have become converted into calcified cylinders (Urban, Zeldenrust, Turner). Sudden fatal haemorrhage from angiomas is not unusual, as in Turner's case and the following case.

Case IV—Female 35. Sudden onset of rapidly fatal coma. cerebrospinal fluid blood stained. *Necropsy*—Spongy haemorrhagic area 3 centimetres in diameter in anterior part of right internal capsule. all other organs normal. *Histology*—Typical cavernous angioma with recent thrombosis and haemorrhage. periphery shows many small calcified vessels.

Other anomalies of the nervous system may be associated with angiomas, e.g. syringomyelia (Russell, Wolf and Wilens). In Wolf and Brock's second case an arterio venous angioma of the frontal lobe was continuous through a deficiency of the bone with an angiomatous mass beneath the skin. Associations with cutaneous or visceral angiomas or other anomalies are described later.

(e) *Peripheral nerves*

Nerves are rarely the site of angiomas. Purcell and Gurdjian saw a cavernous angioma of the sciatic nerve in an infant, and referred to occasional earlier records. Bergstrand described an angioma of the tibial nerve in a man aged 31 but his contention that this was malignant and had metastasized to the lungs cannot be accepted, the lung tumours were of quite different structure.

(f) *Viscera*

The well-known cavernous angiomas of the *liver* need no description here, noteworthy however, is their loss of vascularity and conversion into fibroma like areas, as described by Merkel. Multiple or diffuse angiomatosis of the *liver* is occasionally seen in infants, sometimes with and sometimes without similar lesions in the spleen, lungs, skin or other parts (Falkowski, Foot, Orzechowski, Taylor and Moore, and see Fig. 346). Small cavernous angiomas of the *spleen* are not rare, they are prone to cystic changes and intra cystic haemorrhages and I think it likely that most non epithelial splenic cysts arise in this way. Angiomas of the *intestine* have been reported by Merchant and by Lockhart Mummery, of the *kidney* by Swan and Balme, of the *adrenal* by Menon and

(c) *Bones*

Haemangiomas of bones were carefully studied by Bucy and Capp who found that these lesions were nearly all of the cavernous type that their most frequent sites were the vertebrae and skull and that radiographically they produced rather distinctive appearances. In flat bones like the skull scapula and pelvis, a prominent sun burst appearance due to new formed bone trabeculae radiating from the surface of the bone is usual, in vertebrae, prominent vertical trabeculation and in tubular bones loculated expansive lesions. Other noteworthy papers are those of Makrycostas Scherer Karshner *et al* and Pulvertaft on vertebral angiomas, and of Anspach Pich and Kaplan and Kanzer on the 'sunray' angiomas of the skull. The latter have often been misdiagnosed 'sarcoma' from their radiographic appearances but they are benign lesions.

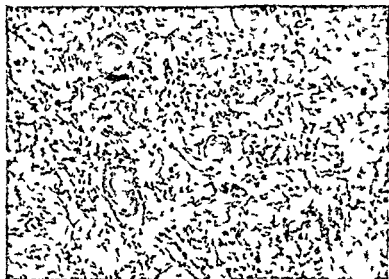


FIG. 345.—Capillary angioma of cerebellum showing a meshwork of vasoformative tissue largely non-canalized traversed by some larger vessels which have undergone thrombosis ($\times 120$).

which as in Anspach's case may remain stationary for many years. A peculiar tumour of a child's skull possibly related to the 'sunray' angiomas is described as Case I Chapter 43.

(d) *Central nervous system*

In their monograph¹ in 1928 Cushing and Bailey divided vascular growths of the brain into two main groups—angiomatous malformations and haemangioblastomas or true tumours. The former include capillary cavernous venous and arterial malformations comparable with those of the skin. The commonest of the haemangioblastomas are those occurring in the cerebellum in young adults: the tumour consists of a mass of tangled small vessels or vasoformative tissue either solid or cystic (Fig. 345) often with only a relatively small nodule or plaque of growth in the wall of a large cyst (Urban, Cox and Trumble). Capillary angiomas of the cerebrum are rare (Barnard and Walshe).

Although many subsequent workers have found Cushing and Bailey's

(c) *Coexisting multiple angiomas of skin and enchondromas of bones (Ollier's disease)*

This rare association, "Kast's syndrome", has been reviewed by Carleton and Robb-Smith and by Carleton *et al*, who described a woman aged 32 with multiple enchondromas of the hands and multiple haemangiomas of the skin and subcutaneous tissues and of several bones. Of the few recorded cases, most have been males.

(d) *Coexisting angiomas of skin and central nervous system or its coverings*

(See Cushing (1906), Cobb, Rogers, Peters and Tebelis, Cox and Trumble, Karshner *et al*, Nussey and Miller). In these cases the presence of vascular naevi on the face or elsewhere points to the nature of the central nervous lesion. The nervous and cutaneous lesions often affect the same segmental level, e.g. facial naevi accompany cerebral lesions, and the level of trunk naevi corresponds to that of the growths affecting the spinal cord. Specially associated with the names of Sturge, Weber and Kalischer is a group of cases showing facial and leptomeningeal naevi, accompanied by radiographically visible calcification of the brain, and often by epilepsy, mental retardation and glaucoma. In Wolf and Brock's third case, a facial naevus coexisted with extensive venous angiomatosis of the retina, optic nerve, cavernous sinus, base of cerebrum, brain stem and cerebellum.

(e) *Coexisting angiomas of retina and central nervous system and visceral abnormalities*

(See Lindau, Collier, Davison *et al*). The complete syndrome, often called Lindau's or von Hippel-Lindau's disease, comprises angiomatosis of the retina, angiomas of the central nervous system usually of the cerebellum, and various visceral lesions including cysts of the pancreas or kidney and renal adenoma. In some instances, as in Collier's cases, angiomas of the brain coexist with visceral lesions but retinal angiomas are absent. The case described by Wolf and Wilens showed a cystic angioma of the cerebellum, three small angiomas of the spinal cord, syringobulbia and syringomyelia, cysts of pancreas and kidneys, adenoma of the kidney, aberrant adrenal tissue in a retroperitoneal lymph gland and three chromaffin tumours of the left adrenal gland. Lindau's disease is familial in about 20 per cent of cases, some members of a family may have retinal lesions, some brain lesions and some the complete syndrome.

(3) *Lymphangiomas*

"Cystic hygroma" of the neck or axilla has excited the interest of pathologists since Wernher's account (cited by Goetsch) in 1843. Treves described a huge hygroma which extended from the floor of the mouth to the lower rib margin in an infant 3 weeks old. Goetsch's paper contains an admirable review of the subject and a detailed study of 12 cases.

(a) *Site*

The favourite sites of lymphangiomas are the neck and axilla, but they occur also in the arm, mediastinum, mouth region and abdomen. Perlmann

Annamalai of the *omentum* by Stout and Cassel, of the *placenta* by Strachan and by Marchetti

(2) Multiple haemangiomatous syndromes

Vascular hamartomas in a single tissue such as the skin or central nervous system are often multiple, e.g. in 16 per cent of patients with angiomas of the skin (Fitzwilliams). But two or more different tissues such as the skin and nervous system or the spleen and liver may be affected simultaneously. Eponym enthusiasts have made the most of the many possible combinations of sites and combinations of angiomas with other abnormalities. Here it must suffice to give only brief notes and references to the more important syndromes and to refer to Weber's useful outline.



FIG. 346—From a specimen of diffuse extensive angiomatosis of liver of a new born infant. Note the inclusion of bile ducts in the septa between the vascular spaces ($\times 120$).

(a) Hereditary multiple telangiectasis of skin and mucous membranes

(See Osler, Goldstein, McArthur, Schuster and Cappon.) Multiple punctate nodular or spider naevi develop on skin and visceral linings usually during childhood or adolescence, persist throughout life and cause recurring haemorrhages from mucous membranes. The disease is familial and is transmitted by both sexes and behaves as a Mendelian dominant. Schuster saw coexisting multiple aneurysms of the splenic artery and venous anomalies in lungs and liver.

(b) Coexisting angiomas of skin and viscera

These may affect various organs, e.g. skin, liver and spleen (Falkowski), skin, liver and lung (Orzechowski, Taylor and Moore), skin, lungs, thyroid, intestines, etc. (Jaffe), skin, stomach, intestine, kidney and adrenal (Merchant).

lined by epithelium, which has been flattened and disguised in most situations by obstructive distension of the cavities. The presence of lax non distended or ramifying spaces also lined by flat non epithelial cells will usually make the nature of the lesion clear. Microscopical distinction between epithelial and lymphatic cystic growths may sometimes be impossible. Supposedly lymph vascular lesions of even non epithelial organs are sometimes epithelial, thus the "lymphangio endothelioma" of the heart reported by Perry and Rogers was almost certainly an epithelial heterotopia similar to those described by Davidsohn and Rezek.

(b) *Sex and age*

The sexes are nearly equally affected females slightly predominating. Most of the cervical and axillary growths are noticed at birth, but some do not appear until later. Some internal tumours announce themselves early, e.g. in Case V above but many of them are not discovered until adult life, and many of those discovered late show dense fibrous walls and septa and other signs of long duration and quiescence.

(c) *Structure and growth*

Goetsch gives a full account with many good figures, and interprets the growth of hygroma as follows: "Endothelial fibrillar membranes or sprouts from the walls of the marginal cysts penetrate the adjacent normal tissues. A lymph-like fluid is secreted within the fibrillae, which are thereby caused to spread apart and canalize. Minute cysts with an endothelial lining are thus formed within these sprouts. By continued secretion within, the cysts enlarge, by pressure atrophy of the walls between adjoining cysts, the large cavities characteristic of hygroma are formed." The extending cystic lesion mingles with or invests neighbouring nerves, muscles or other structures. Goetsch points out how this mode of growth resembles that of the developing lymphatic system.

Other noteworthy features in the hygromas of the neck and axilla which I have studied have been (i) the abundance of irregularly distributed smooth muscle in the walls of many of the larger channels, similar to that seen in haemangiomas (e.g. Cases I and III above), (ii) the frequent presence of patches of lymphoid tissue as an integral part of the growths, and (iii) the frequent presence of many large or irregular blood vessels mingled with the lymphatic spaces suggesting that haemangiomas and lymphangiomas may not be sharply separable but that lesions of mixed structure occur.

(d) *Malformation or neoplasm?*

Goetsch believed that the mode of extension which he described shows hygroma to be a true infiltrating neoplasm and not merely an enlarging cystic malformation. In my opinion, however, fluid accumulation, the progressive formation of collateral channels and in some cases supervening thrombosis and organization, suffice to account for the growth of hygromas. The mingling of the lymphatic channels and cysts with the involved tissue is not a proliferative invasive process, but merely a necessary feature of a vascular malformation comparable with that seen in haemangiomas. Like haemangiomas, lymphangiomas are often known to be

reported a lymphangioma in the kidney and Rabson and Zimmerman one in the adrenal, and I have seen the following examples in the mesentery pancreas, kidney and epididymis

Case V—Female aged 4 years and 8 months Recent abdominal pain laparotomy—rounded lobulated tumour 12 centimetres in diameter situated in mesentery closely contiguous with bowel a loop of which had to be removed with tumour This consists of honeycomb of large and small cysts with watery fluid *Histology*—Cysts devoid of epithelium and lined by flat cells fibrous septa contain similar small ramifying clefts

Case VI—Female aged 67 Abdominal mass noticed for 3 years not enlarging Removal of kidney with well defined tumour 15 centimetres in diameter replacing a small part of centre of organ and projecting laterally from it This shows a honeycomb of large and small cysts separated by fibrous septa and containing watery fluid *Histology*—Cysts everywhere lined by flat non-epithelial cells

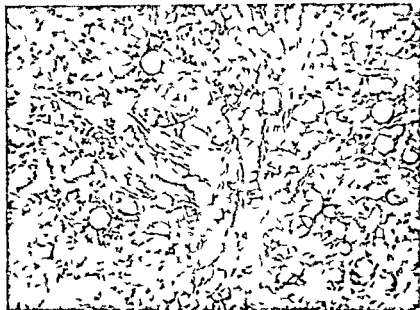


FIG 347—*Case VIII* Lymphangioma of epididymis ($\times 120$)

Case VII—Female aged 87 Incidental necropsy finding a well-defined honeycomb cystic mass 8 centimetres in diameter in head of pancreas microscopically similar to that in previous case

Case VIII—Well-defined firm white growth 2 centimetres in diameter was excised from epididymis of elderly man who had noticed it slowly enlarging for 2 years *Histology* (Fig 347)—Tumour consists of a honeycomb of rounded or elongated spaces 10 to 40 μ in diameter lined by large flat polygonal cells and separated by a variable amount of dense fibrous tissue The spaces appear empty containing no blood corpuscles or obvious secretion (Compare with specimens depicted as epididymomata by Baillie)

Needless to say great caution is needed before diagnosing as lymphangiomatous a cystic growth in an epithelial organ very thorough microscopical study of many parts must be undertaken in order to exclude the possibility of the cysts being

The following is a typical example

Case IX—Male, aged 22 Painful purplish red dome shaped mass 1.5 centimetres in diameter present for many years on anterior aspect of middle third of right shin. excision of mass which involved only skin and subcutaneous tissue. *Histology* (Fig. 348)—Many



FIG. 348—*Case IX* Glomangioma. A = large and small vascular channels with zones of glomus cells in their walls. B = a large mass of glomus cells ($\times 100$)

well formed large vascular channels contained plentiful closely packed polyhedral cells in their walls arranged either in even strata separated from the lumina by a layer of intima or in large irregularly distributed masses between the vessels

present at birth, and many of those not discovered until adult life as in Cases VI VII and VIII, show clear structural evidence of old age and quiescence

TRUE ANGIOBLASTIC NEOPLASMS

We come now to the difficult question do truly neoplastic angiomatous growths occur? I have seen no evidence to lead me to alter the opinions reached in my 1934 work, which were briefly that, while malignant angioblastic growths probably do occur and sometimes produce blood borne metastases they are very rare and most supposed examples are either multifocal hamartomas or vascular tumours of other kinds. Additional to the cases reviewed in 1934, those subsequently described by Robinson and Castleman and by Stout support the view that genuine angioblastomas or at least mesenchymal tumours with pre dominant vasoformative qualities do occur. I am less satisfied regarding the tumours reported by Hall Ogilvie and Mackenzie (second case) and Murray and Stout which may have been only vascular sarcomas of other kinds. In Hewer and Kemp's case of haemangio endothelioma of the heart, the supposedly metastatic tumours in the lungs and elsewhere may well have been like the cavernous angiomas of the oesophagus and liver which were present, benign multifocal lesions. The angioblastoma of the spleen with metastases in the liver described by De Navasquez resembled those of Jores Wright and others which as suggested in my 1934 work may be interpreted as multifocal 'system' lesions rather than as metastasizing neoplasms. However that metastasis may be the correct interpretation of these cases cannot be excluded.

The conclusion that true tumours of vasoformative tissue indeed exist does not imply that these are to be distinguished sharply from other mesenchymal tumours. Let us recall once again the intermutability of the various mesenchymal tissues the close kinship of their tumours and the fact that vascular tissue is of all the mesenchymal tissues the most ubiquitous and one of the most plastic. Then we will be prepared to regard true angiomas and angiosarcomas not as fixed species but merely as conspicuously vasoformative variants of the genus mesenchymoma.

ANGIOMAS AND ANGIOMATOID HAMARTOMAS IN ANIMALS

Feldman (Chapter XI) gives references to many haemangiomas and a few lymphangiomas in horses, cattle and dogs rarely in other species. Nieburle and Cohrs refer to or depict multiple cavernous angiomas of the lung of the ox of the intestine of the horse of the liver in the ox horse sheep cat dog and fowl and of the bladder in the horse. As in man, so in animals, probably most angiomas are hamartomas rather than true tumours but true neoplasia and metastasis certainly occur. Rudduck and I examined 2 cavernous angiomas of the skin in fox terriers an angiosarcoma of the wing of the atlas with metastases in the lungs in a greyhound an angiosarcoma of the buttock in a Scottish, and diffuse angiomatosis of the liver in a male chinchilla cat aged 3 years.

GLOMANGIOMA

For detailed accounts and reviews of this tumour see Masson Mackey and Lendrum Freudenthal *et al* Stout Lendrum and Mackey, and Murray and Stout

- Baillie, M (1936) *Proc Roy Soc Med* 29 367
- Barnard W G, and Walshe, F M R (1931) *J Path Bact*, 34 385
- Bergstrand H (1934) *Amer J Cancer* 21 588
- BUCY, P C, and CAPP, C S (1930) Primary hemangioma of bone, *Amer J Roent* 23 1 (An excellent radiographic and pathological study)
- Cappon D (1945) *Brit Med J* i 440
- Carleton A, and Robb Smith A H T (1939) *Proc Roy Soc Med*, 32 266
- Carleton, A, Elkington J St C, Greenfield J G and Robb Smith A H T (1942) *Quart J Med* 11, 203
- Cobb S (1915) *Ann Surg* 62 641
- Collier W T (1931) *Brit Med J* ii 144
- Cox L B and Trumble H C (1939) *Med J Austral*, ii 308
- Cushing H (1906) *J Amer Med Assoc* 47 178
- CUSHING, H and BAILEY, P (1928) *Tumors Arising from the Blood Vessels of the Brain* Baltimore
- Davidsohn I (1938) *Arch Path* 26 422
- Davison C, Brock, S and Dyke C G (1936) *Bull Neurol Inst NY* 5, 72
- Ewing J (1940) *Neoplastic Diseases* Philadelphia
- Falkowski, A (1914) *Beitr path Anat* 57 385
- Feldman W H (1932) *Neoplasms of Domesticated Animals* Philadelphia
- Fitzwilliams D C L (1911) *Brit Med J* ii 489
- Foot N C (1927) *Amer J Path* 3 653
- Freudenthal W, Anderson R G and Weber F P (1937) *Brit J Derm*, 49 151
- GOETSCH, E (1938) Hygroma colli cysticum and hygroma axillare, *Arch Surg* 36 394 (A well illustrated study and review)
- Goldstein H I (1932) *Arch Derm Syph* 26 282
- Goldstein H I (1936) *Brit Med J* i 721
- Hall, E M (1935) *Amer J Path* 11 343
- Harvey, W F, Dawson E K and Innes J R M (1940) *Edinb Med J* 47 513
- Hewer T F and Kemp R P (1936) *J Path Bact* 43 511
- Jaffe R H (1929) *Arch Path* 7 44
- Jenkins H P and Delaney P A (1932) *Surg Gyn Obst* 55 464
- Jores L (1908) *Zbl allgem Path* 19 662
- Kaplan A and Kanzer M (1939) *Arch Surg* 39 269
- Karshner R G, Rand C W and Reeves D L (1939) *Arch Surg* 39, 942
- LENDRUM, A C, and MACKEY, W A (1939) 'Glomangioma', *Brit Med J* ii 676 (A useful outline with 17 case reports)
- LINDAU, A (1926) Studien über Kleinhirncysten Bau pathogenese und beziehungen zur angiomatosis retinae *Acta Path Microbiol Scand* Suppl
- Lindau A (1931) *Proc Roy Soc Med* 24 363
- Lockhart Mummery J P (1938) *Proc Roy Soc Med*, 31 694
- MacDermott E N (1935) *Brit J Surg*, 23 252
- Mackey W A and Lendrum A C (1936) *Brit J Surg* 24 208
- Mailer R (1935) *Brit J Surg* 23 245
- MAKRYCOSTAS, K (1927) Über das wirbelangiom lipom und osteom *Virchows Arch* 265 259 (A valuable study of small benign angiomas found on routine section of vertebrae)
- Marchetti A A (1939) *Surg Gyn Obst* 68 733
- MASSON, P (1935) Les glomus cutanes de l'homme *Bull Soc franç Derm* 42 1174 (The most detailed account of glomus tumours)
- McArthur G A D (1937) *Med J Austral* i 780
- Menon T B and Annamalai D R (1934) *J Path Bact* 39 591
- Merchant F T (1939) *Arch Surg* 39 1031
- Merkel H (1904) *Beitr path Anat* 36 574
- Murray M R and Stout, A P (1942) *Amer J Path* 18 183
- Murray M R and Stout A P (1944) *Ibid* 20 277
- De Navasquez S (1936) *J Path Bact* 42 651
- Nieberle K and Cohrs P (1931) *Lehrbu h der Spez Path Anat der Haustiere* Jena
- Nussey A M and Miller H H (1939) *Brit Med J* i 822

(1) Origin and site

Masson's discovery of the neuro myo arterial glomera of the skin and subcutaneous tissues and his demonstration of these as the source of the tumours now called glomangiomas have been fully confirmed by later workers. The normal glomus is now recognized as a convoluted arteriolar venous anastomosis with a characteristic cellular wall containing a thick layer of cuboidal epithelium like cells. Murray and Stout have advanced strong evidence that these epithelioid cells are identical with the capillary pericytes of Zimmermann which are akin to the muscle cells of arterioles. The tumours are usually small and well defined rarely more than 2 or 3 centimetres in diameter usually single but sometimes multiple. They have occurred in adults of all ages but only rarely in children. Harvey *et al* depict a glomangioma present since infancy in a girl aged 7. Glomera have been demonstrated most abundantly in the integuments of the peripheral parts of the limbs and these are the commonest sites also of the glomus tumours. The undoubted occurrence of similar tumours of the penis trunk face and more rarely of muscles and other deeper tissues, shows that glomera are of wider distribution than was at first supposed.

(2) Structure

The growth consists of cavernous vascular spaces the walls of which contain even layers or irregular masses of the characteristic glomus cells. These are uniform in size polyhedral have central rounded darkly staining nuclei 7-10 μ in diameter and are usually separated by distinct cell walls. Transitions from cuboidal glomus cells to spindle cells indistinguishable from smooth muscle fibres are sometimes to be seen a point which accords with the view that glomus cells are identical with Zimmermann's pericytes. Glomangiomas may include extensive masses of glomus cells traversed by only scanty vascular channels or, on the other hand they may show predominant vascular structure with only scanty cuboidal cells in the walls of cavernous spaces. Between the vascular spaces lie varying amounts of connective tissue with or without smooth muscle fibres and nerves are often to be seen at the periphery or in the septa of the tumours.

(3) Growth and behaviour

Glomangiomas constitute one variety of the group of lesions formerly designated painful subcutaneous tubercle which included also painful leiomyomas neurofibromas and inflammatory nodules. Because of the severe paroxysmal pain which often attends them especially when situated on the limbs, glomangiomas are usually removed while still quite small. They are usually well-circumscribed slowly enlarging benign lesions, but Murray and Stout reported an infiltrating recurrent growth of this kind. Excision of the growth abolishes the attacks of pain.

REFERENCES

- Anspach W E (1937) *J Amer Med Assoc* 108 617
Bailey O T and Ford R (1942) *Amer J Path* 18 1
Bailey P and Bucy P C (1931) *Amer J Cancer* 15 15

with the formation of an external boss on the skull vault or of a similar exostosis in the orbit or nasal cavity. The following case provided an interesting example of invasion of bone by a plaque-like meningioma.

Case II—(Mr H C Trumble's case) A woman aged 50 had noticed unilateral exophthalmos and swelling in temporal fossa for many months. Skiagrams showed great thickening of temporal bone lesser wing of sphenoid etc. Operation disclosed flat plaque like growth forming velvety layer up to 4 millimetres thick on inner surface of dura over an irregular area of 4 centimetres in main extent with multiple patches of growth in the area. the dura was stripped and part of the bone removed. *Histology* (Fig. 350)—Typical moderately cellular whorled meningioma invading dura and bone.

(2) Microscopic structure

Like other kinds of mesenchymal tumours, the meningiomas show wide variations of cytology and pattern, and sometimes develop bone or other



FIG. 351.—Epithelioid structure in para sagittal meningioma 7 centimetres in diameter from a boy aged 15 ($\times 150$)

kinds of heterotopic tissue. Bailey and Bucy proposed to distinguish 9 types of growth—mesenchymal, angioblastic, meningoepitheliomatous, psammomatous, osteoblastic, etc. However, these are not distinct types but merely variants of the single entity meningioma. The variability of cell form and growth pattern of meningeal tissue in culture, revealed by Cox and Cranage's and by Bland and Russell's studies, accords with the structural gradations and combinations seen in the tumours. These are as follow (Figs 351–356)

(a) Epithelioid form

Closely packed plump polyhedral or elongated cells form well defined epithelium like clumps, often with a whorled arrangement of the cells, set in a vascular connective tissue stroma.

- Ogilvie R F and Mackenzie I (1936) *J Path Bact* 43 143 and 429
- Orzechowski G (1928) *Virchows Arch* 267 63
- OSLER, W (1907) On multiple hereditary telangiectases with recurring haemorrhages ,
Quart J Med 1 53
- Perlmann S (1928) *Virchows Arch* 268 524
- Perry C B and Rogers H (1934) *J Path Bact* 39 281
- Peters G and Tebelis F (1937) *Z ges Neurol Psych* 157 782
- Pich G (1938) *Beitr path Anat* 101 181
- Pulvertaft R J V (1938) *J Path Bact* 47 101
- Purcell F H and Gurdjian E S (1935) *Amer J Surg* 30 541
- Rabson S M and Zimmerman E F (1938) *Arch Path* 26 869
- Rezek P (1938) *Virchows Arch* 301 305
- Robinson J M and Castleman B (1936) *Ann Surg* 104, 453
- Rogers L (1933) *Brit J Surg* 21 229
- Russell D S (1932) *J Path Bact* 35 103
- Scherer E (1933) *Beitr path Anat* 90 521
- Schuster N H (1937) *J Path Bact* 44 29
- Stout A P (1939) *Amer J Cancer* 36 25
- STOUT, A P (1943) Hemangio-endothelioma a tumor of blood vessels featuring vascular endothelial cells *Ann Surg* 118 445 (A useful review and case reports)
- Stout A P and Cassel C (1943) *Surgery* 13 578
- Strachan G I (1923) *J Obst Gyn* 30 433
- Swan R H J and Balme H (1935) *Brit J Surg* 23 282
- Taylor, A C and Moore E (1933) *Amer J Cancer* 19 31
- Treves F (1881) *Trans Path Soc Lond* 32 194
- Turner, O A (1937) *Arch Path* 24 223
- Urban H (1926) *Z ges Neurol Psych* 155 798
- WEBER F P (1946) Some telangiectatic and other anomalous vascular groups especially those of dysplastic origin from *Rare Diseases* p 49 London (A useful clinical survey of the main multiple angiomatoid lesions)
- Weiss A (1933) *Frankfurt Z Path* 44 144
- Willis R A (1934) *The Spread of Tumours in the Human Body* London
- Wolf A and Brock S (1935) *Bull Neurol Inst NY* 4 144
- Wolf A and Cowen D (1936) *Bull Neurol Inst NY* 5 485
- Wolf A and Wilens S L (1934) *Amer J Path* 10 545
- Wright A W (1928) *Amer J Path* 4 507
- Zeldenrust J (1938) *Amer J Cancer* 34 234

(c) *Psammoma form*

More or less plentiful calcified spherules are scattered through growths of the preceding forms. Many of these spherules occupy the centres of whorls,

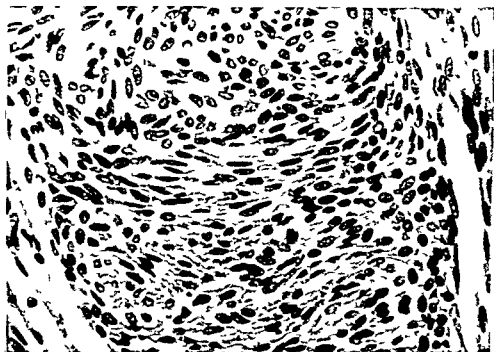
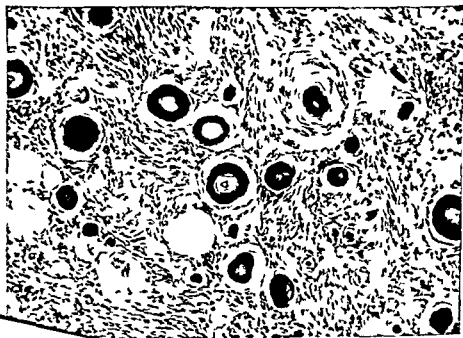


FIG. 354—Detail of Fig. 353 ($\times 400$)



meningioma with calcified spherules from thoracic part of the spinal cord ($\times 120$)

them or in non-whorled areas, they often show regular calcification commences both within tumour cells and old centres of whorls, and only occasionally in the walls

(b) *Whorled spindle celled form*

Plump spindle cells are arranged in contiguous whorls which however are not sharply circumscribed but coalesce at their margins. The whorls range from



FIG. 352.—Epithelioid structure with small whorls in a meningioma from a man aged 40 ($\times 150$)

20μ to 100μ or more in diameter. They sometimes contain small central blood vessels but are much more often solid throughout. Collagen fibres are sparsely



FIG. 353.—Whorled but non-calcified meningioma ($\times 90$)

mingled with the whorled tumour cells but the central parts of whorls often undergo conversion into hyaline spherules of collagen.

(g) Sarcomatous form

Diffusely cellular growths, devoid of calcification and with only slight or no signs of whorling, are not rare. When these signs are completely lacking it is impossible to be sure of the meningiomatous nature of the tumour.

Again it must be stressed that the foregoing are not distinct kinds of growths but merely structural variants, combinations or transitional structures are often seen in one tumour, particularly the forms (a) to (e). Other occasional structural features are aggregations of lymphoid cells or of lipid foam cells.

GROWTH AND BEHAVIOUR

(1) Rate of growth

The rate of growth varies greatly. Some patients have symptoms for many years before operation, or long periods elapse between removal of the tumour and recurrence, in other cases the symptoms are of brief duration and rapidly progressive, or promptly recurrent growth quickly attains a large size. The most indolent growths are of types (b) to (e) above, the more active ones of types (a) (f) and (g). Mitotic figures are scanty in most meningiomas.

(2) Invasiveness

While most meningiomas are "benign" in that they are slowly growing circumscribed tumours curable by adequate local removal, others are malignant in that they invade surrounding tissues and on rare occasions metastasize. These could properly be called 'meningiosarcomas'.

(a) Invasion of the skull

This takes place in perhaps 1 in 5 of the clinically important intracranial meningiomas. The growth extends into the bone canals and diploic spaces and usually excites osteoplastic thickening and the formation of an external boss composed of new-formed bone permeated by meningiomatous tissue. Good reviews and case reports include those of Cushing, Penfield, Rand, Cope, Grant, Taylor, Kolodny, Bernstein, Rowbotham and Money. Most meningiomatous hyperostoses occur in the vault of the skull, but the orbital plates and other parts of the base may be affected (Winkelman, Meadows and Case II above). Rarely, as in cases described by Cushing and by Grant, meningiomas extend beyond the bone and infiltrate surrounding soft tissues such as the temporal muscle. Spinal meningiomas do not cause vertebral hyperostoses, because the dura is unattached to the bone.

(b) Invasion of the brain

Invasion of the brain, chiefly along the perivascular spaces is less frequent. I have seen it in two cases and it is depicted by Bernstein and by Kalbfleisch and Grebe, who also saw invasion of the Gasserian ganglion.

(c) Invasion of the dural venous sinuses

This was observed by Towne and by Kalbfleisch and Grebe. In one of Towne's cases the growth extended down the jugular and innominate veins into

of small blood vessels. Hence the grains are nearly all spherical and only rarely cylindrical, they are similar to the sand grains of the normal meninges, pineal gland, choroid plexus and brain. Some calcified meningiomas are plainly visible in skiagrams.

(d) *Fibrous form*

Some tumours are predominantly fibro collagenous, with or without whorling or sand grains and microscopically resembling hard less often soft fibromas. Collagen fibroglia and elastic fibres are present. Dense hyaline change is frequent, either in discrete spherules or in irregular trabeculae.

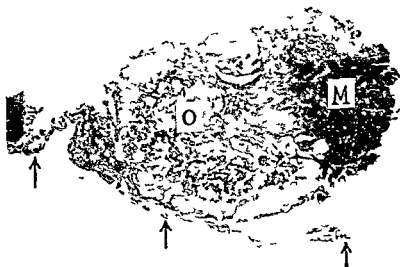


FIG 356—Case III. Ossified meningioma. M = meningiomatous part. O = ossified part. Arrows denote spinal dura mater. ($\times 4$)

(e) *The ossified form*

This is exemplified in the following case:

Case III—Female 41. Surgical removal of hard well defined ovoid intrathecal tumour 1.5 centimetres in diameter. *Histology* (Fig 356)—One half of tumour consists of typical rather cellular meningioma of fibrous type with many scattered psammoma bodies; the other half of osteoid tissue and bone with areas of haemopoietic bone marrow. Transitions from meningiomatous to bony tissue are evident, early ossification proceeding especially in psammomatous foci.

(f) *Angiomatoid form*

Some tumours are richly vascular showing plentiful thin walled vessels irregularly distributed through more diffusely cellular growth. All gradations are seen between typical meningiomas and predominantly angiomatous growths (Wolf and Cowen).

- Kernohan J W (1941) *Arch Path* 32 843
- Kolodny A (1929) *Surg Gyn Obst*, 48, 231
- Laas E (1935) *Beitr path Anat* 95 431
- LEARMONTH, J R (1927) On leptomeningiomas (endotheliomas) of the spinal cord ,
Brit J Surg 14 397
- Mallory F B (1920) *J Med Res* 41 349
- Meadows S P. (1944) *Proc Roy Soc Med* 38 594
- Money R A (1943) *Med J Austral*, 1 184
- Oberling C (1922) *Bull Assoc franç Cancer* 11, 365
- Penfield W G (1923) *Surg Gyn Obst* 36, 657
- Penfield W G (1932) *Cytology and Cellular Pathology of the Nervous System* Vol III p 959
New York
- Power D A (1886) *Trans Path Soc Lond* 37 12
- Rand C W (1923) *Arch Surg* 6 573
- ROWBOTHAM G F (1939) The hyperostoses in relation with the meningiomas ,*Brit J Surg* 26 593 (A well illustrated account and review)
- Russell W O and Sachs, E (1942) *Arch Path* 34 240
- SCHMIDT, M B (1902) Ueber die Pacchioni schen Granulationen und ihr Verhältniss zu den Sarcomen und Psammomen der Dura Mater ,*Virchows Arch* 170, 429 (The classical demonstration of the arachnoid origin of meningiomas)
- Taylor J (1928) *Brit J Surg* 16 6
- Towne E B (1926) *Ann Surg* 83 321
- WEINBERGER, L M (1940) The diffuse meningiomatoses *Amer J Cancer* 38 1
- Willis R A (1938) *J Path Bact*, 47, 253
- Winkelman N W (1930) *Arch Neurol Psych* 23 494
- Wolf A and Cowen D (1936) *Bull Neurol Inst NY* 5 485

the superior vena cava. Local protrusions of parasagittal growths into the superior longitudinal sinus are not unusual when searched for, I have seen several examples in surgically removed specimens (See also Fig 350)

(3) Metastasis

In view of the invasion of the venous sinuses by meningiomas, metastasis to the lungs might be anticipated. Actually however, this occurs only very rarely. The clearest examples are those reported by Jurow and by Hamblet. In a negress aged 72 who died of pneumonia Jurow found two microscopically typical intracranial meningiomas with multiple small metastases of similar structure (including granular calcification) in the lungs. Hamblet saw 8 metastatic nodules of meningioma in the liver of a Chinese male aged 41. Jurow cited several other reported instances but none as conclusive as his own. Another possible example of pulmonary metastasis from meningioma was that reported in 1886 by Power a woman aged 25 who had had hemiplegia and fits for many years was found to have a fibrosarcoma of the dura excavating the brain and eroding the parietal bone and a small tumour of similar structure at the apex of the left lung.

The diagnosis of the four tumours reported by Russell and Sachs as fibrosarcoma of arachnoidal origin with metastases is dubious. The tumour in their first case was almost certainly carcinoma of the lung in their second case a huge hepatic tumour may have been the primary one and in their third and fourth cases the anaplastic growths involving both brain and meninges are of uncertain nature.

REFERENCES

- Basley P. and Bucy P. C. (1931) *Amer J Cancer* 15 15
 BERNSTEIN S. A. (1933) Über das Verhalten des Schädelknochens beim Duraendotheliom. *Virchows Arch* 290 501 (A well illustrated account of cranial hyperostoses with many references)
 BLAND J. O. W. and RUSSELL, D. S. (1938) Histological types of meningiomas and a comparison of their behaviour in tissue culture with that of certain normal human tissues. *J Path Bact* 47 291
 Brown M. H. and Kernohan J. W. (1941) *Arch Path* 32 651
 Cope Z. (1924) *Brit J Surg* 12 794
 Cox L. B. and Cranage M. L. (1937) *J Path Bact* 45 477
 Cushing H. (1922) *Arch Neurol Psych* 8 139
 CUSHING H. (1922) The meningiomas (dural endotheliomas) their source and favoured seats of origin. *Brain* 45 282
 Davis F. A. (1940) *Arch Ophth* 23 735 and 957
 Elsberg C. (1928) *Surg Gyn Obst* 46 1
 Gardner W. J. and Turner O. A. (1939) *Surg Gyn Obst* 66 804
 Goar E. L. (1927) *Contributions to Ophthalmic Science* p 285
 Grant F. C. (1925) *Ann Surg* 81 1036
 Hamblet J. B. (1944) *Arch Path* 37 216
 HOSOI K. (1930) Meningiomas with special reference to the multiple intracranial type. *Amer J Path* 6 245
 Innes J. R. M. Harvey W. F. and Dawson E. K. (1938) *Edinb Med J* 45 855
 Jurow H. N. (1941) *Arch Path* 32 222
 KALIBFLISH H. H. and GRUBE, H. (1937) Über das Einwachsen der Schädelmeningiome in das umgebende Gewebe namentlich in das Gehirn. *Arch klin Chir* 188 118 (A good account of 7 invasive meningiomas)

suggests the possibility that hormonal disturbances may play a part in the genesis of myomas. This supposition is supported also by the frequent multiplicity of

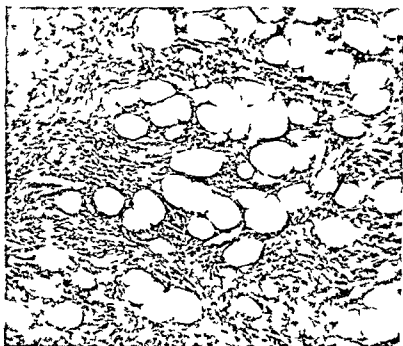


FIG 357 —Fat cells in a uterine myoma ($\times 60$)

the growths, their usual development during the sexually active period of life, their frequent presence in patients with oestrogenic tumours of the ovary (see Chapter 29), and possibly by the experimental production of uterine and peritoneal



FIG 358 —Epithelioid appearances and hyaline change in a uterine myoma ($\times 150$)

“fibroids” (doubtfully related to human myomas however) by prolonged administration of oestrogens (see Chapter 4). There is need of further careful

LEIOMYOMA AND LEIOMYOSARCOMA

THE TUMOURS of non striated muscular tissue will be considered briefly under the following regional heads those of (a) the uterus (b) the alimentary canal, (c) the skin (d) other parts

LEIOMYOMA AND MYOSARCOMA OF THE UTERUS

Adequate descriptions of the main characters of the common uterine myomas are given by many writers e.g. Bland Sutton or Novak and need not be repeated here I comment only on certain special points

(1) Some peculiarities of structure of myomas

(a) *Heterotopic tissues in myomas*

Myomas occasionally show fat cells mingled with the muscular tissue and these sometimes become so abundant that the tumour appears to the naked eye like a lipoma rather than a myoma (Bland Sutton Williamson and Brockman, and Fig 357) Calcified myomas rarely undergo ossification (Glendinning)

(b) *Peculiar appearances of altered muscle fibres*

These occur especially in oedematous or cystic myomas by contraction of groups of muscle fibres into compact masses of plump rounded or ovoid cells or by hyaline collagenous change isolating groups of altered muscle fibres The appearances produced may superficially resemble those of epithelial masses (Fig 358), but transitions between the altered tissue and more typical bundles of muscle fibres are usually to be found

(c) *The relationships of myomas to the surrounding myometrium*

These deserve closer study The usual view that myomas are encapsulated growths sharply distinct from the myometrium needs revision for while this may be true of large tumours it certainly does not apply to many small ones Minute myomas even when apparently well circumscribed to the naked eye are often not sharply separable from the surrounding muscle microscopically the appearances suggesting rather that the early growth of the tumours involves extending myomatous transformation of a small region of myometrium as well as intrinsic proliferation Benign myomas are not invasive in the strict sense but they sometimes form polypoid projections still clothed by intima, within veins (Seyler) Frank's use of the term fibromyosis to describe a peculiar plexiform endolymphatic growth is unfortunate in that it implies a myometrial origin the growth in question more closely resembles endometrial stroma

(2) Evidence of hormonal factors in the causation of myomas

The endocrine control of the structure and activity of the myometrium at once

The following three necropsy cases illustrate these and other features of the disease

Case I (Willis 1934 p 438)—Female 46 *History*—Hysterectomy at end of 1929 for fibroids, then well until September 1931 when cough and pain in chest developed *Necropsy* (May, 1932)—Huge tumour replacing middle lobe of right lung a small tumour in left lung All other organs clear *Histology*—Well differentiated leiomyosarcoma (Fig 359)

Case II (Willis 1934 p 438)—Female, 28 *Necropsy*—Leiomyosarcoma of uterus with metastases in peritoneum liver rib and cranial dura mater



FIG 360—*Case III* Pleomorphic-celled part of uterine leiomyosarcoma ($\times 180$)

Case III (Willis 1941 No 392)—Female 47 *History*—During convalescence from hysterectomy for fibroids patient complained of pain in back and skiagram showed destructive lesions in lumbar vertebrae Re-examination of uterus then disclosed a crescentic area of soft sarcoma in one of the myomas A few weeks later patient died suddenly *Necropsy*—Tumour deposits in retroperitoneal lymph glands whence gross polypoid invasion of ovarian and inferior mesenteric veins and of inferior vena cava large tumour embolus arrested in main left pulmonary artery Multiple metastases in lungs and many vertebrae *Histology*—Parts of growths show well differentiated leiomyosarcoma other parts poorly differentiated pleomorphic-celled sarcoma (Fig 360)

(a) *Age incidence*

Most leiomyosarcomas are in middle aged or elderly people but young women are not exempt (e.g. *Case II*)

(b) *Structure*

The terms 'malignant myoma', 'metastasizing fibroid' etc, which have often been applied to these growths, indicate the high degree of cellular

inquiries into the reproductive and menstrual histories of patients with myomas, into the frequency with which these tumours are associated with significant ovarian abnormalities, and into the frequency of myomas in patients with mammary cancer

(3) Secondary tumours of uterine myomas

Myomas may be invaded by neighbouring growths such as uterine or ovarian carcinomas (Glendining Cullen) or from the peritoneal deposits of gastric or other carcinomas (Schmorl, Davidsohn) or they may be surrounded by such growths but not invaded (Walter). Blood borne metastases from remote primary growths are occasionally found within myomas e.g. from carcinoma of the lung melanoma or mammary carcinoma (Schaper Schmorl and my Case XV Chapter 13)

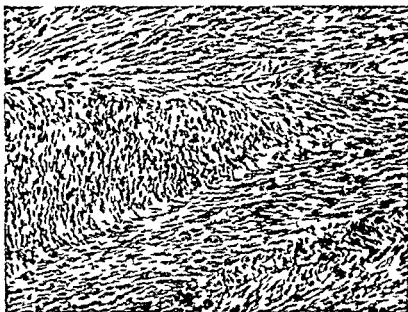


FIG 359—Case 1 From pulmonary metastasis of leiomyosarcoma (150)

(4) Leiomyosarcoma or malignant myoma of the uterus

Most sarcomas of the uterus are myosarcomas and many of these arise in pre existing myomas. The grounds for this conclusion are that in some cases the sarcoma is found in only a part of an otherwise ordinary looking myoma (Case III below) that in nearly all cases of sarcoma the uterus is myomatous and that in not a few of these cases fibroids are known to have been present long before the increase in size or aggravation of symptoms attributable to the sarcoma. In many cases however it is impossible to prove whether the sarcoma arose in a previously benign tumour or whether the tumour was malignant from its inception. In some instances leiomyosarcomatous metastases have developed in patients who had previously undergone hysterectomy for supposedly simple fibroids

good and myofibrils can be clearly demonstrated, distinction between myoma and neurilemmoma may prove impossible. Small firm, well defined pale nodules in the stomach wall are fairly common incidental findings in necropsy work, these are found to be either myomas or neurilemmomas (q v).

Leiomyosarcoma of the stomach is rare, according to Golden and Stout, the proportion of malignant to benign myomatous tumours of the stomach is about 1 to 8.

(2) Myomas and myosarcomas of the intestine

These are rather less common than those of the stomach but a higher proportion of them are sarcomatous (Golden and Stout). The small intestine is more frequently affected than the large intestine, and the most important results are either intussusception with obstruction or ulceration and haemorrhage (Smith, Foshee and McBride, Golden and Stout, Foster). Meckel's diverticulum is an occasional site of origin (Nygaard and Walters). The following Cases IV, V and VI exemplify fatal haemorrhage from benign growths, and Case VII leiomyosarcoma of the large intestine.

Case IV—Female 76. *History*—Admitted to hospital in extremis passing large amounts of fresh blood by bowel and died the following day. *Necropsy*—A smooth spherical tumour 9 centimetres in diameter was attached to middle of small intestine and lay in mesentery. Intestinal mucosa was ulcerated over an area 1.5 centimetres in diameter and a small aperture led from base of ulcer into centre of the tumour which consisted of a thin shell of white tissue enclosing a large degenerated cavity full of blood clot. *Histology*—Benign leiomyoma.

Case V—Female 46. *History*—Several attacks of melaena over a period of 7 months. *Necropsy*—A lateral wall of second part of duodenum contained a firm well circumscribed lobulated tumour 4 centimetres in diameter, hour glass shaped with ulceration of the mucosa overlying the internally projecting half. *Histology*—Benign leiomyoma.

Case VI—Male 47. *History*—Recurrent recent melaena. *Necropsy*—Ovoid tumour 5 centimetres in diameter attached to antimesenteric aspect of ileum 4 feet above caecum, small ulcerated area of growth presented in bowel. *Histology*—Benign leiomyoma with much fibrosis.

Case VII (Willis 1934 p 437)—Male 44 (Chinese). *History*—Constipation and passage of blood and mucus per rectum for 10 months, palliative colostomy. *Necropsy*—Bulky lobulated fairly well defined tumour of rectum with ulceration and perirectal cellulitis, multiple large well defined spherical white metastases in liver only. *Histology* (Fig 361)—Partly well differentiated typical leiomyomatous structure, partly disorderly pleomorphic-celled sarcoma.

LEIOMYOMAS AND MYOSARCOMAS OF THE SKIN

(1) Multiple dermal leiomyomas

These have long been known to dermatologists. They are probably not true tumours but rather hamartomas or minor malformations with excessive development of the *arrectores pilorum* muscles. They often appear at an early age, frequently in regional groups, they grow slowly, seldom to sizes more than 1 centimetre in diameter, and they may remain stationary or retrogress.

differentiation which they may attain. But of course a tumour which invades or metastasizes is a sarcoma, however well differentiated in structure. Moreover in most cases adequate microscopical study of several different parts of a growth will usually lead to a correct diagnosis of innocence or malignancy, sarcomas usually show anaplastic areas with nuclear abnormalities and excessive mitoses. A cellular leiomyomatous growth which arouses the pathologist's suspicion but of the malignancy of which he feels uncertain is usually benign. Much less commonly, a tumour adequately studied histologically and regarded as benign may prove its malignancy by its behaviour. Steiner has reviewed such cases in which a tumour has been composed, ' in both the primary growth and its metastases of benign appearing fully differentiated smooth muscle cells and dense connective tissue but his view that this distinguishes it from primary leiomyosarcomas of the uterus and from sarcomas arising in fibromyomas is unwarranted. Steiner's case was of interest in that, as in my Case I a myomatous uterus not clinically suspected of malignancy produced massive well differentiated metastases in the lungs.

(c) *Metastases*

As with most other kinds of sarcoma the lungs are the principal sites of metastasis. Other organs may, however, be affected e.g. in my cases the liver, bones and dura mater, in Finlay's case the heart and kidney. Lymph nodal deposits were present in the cases of Finlay, Schreine, Steiner and in my Case III.

LEIOMYOMA AND MYOSARCOMA OF THE ALIMENTARY TRACT

Leiomyomas of the *oral cavity* are very rare (Stout). Those of the *oesophagus* are less uncommon as incidental necropsy findings I have encountered 3 specimens, the largest 2 centimetres in diameter in a woman of 52 years. Rose saw 4 oesophageal myomas with obstruction in a man of 74 years. He reviewed 48 reported cases, of which the tumours were recorded as single in 35 and multiple in 11.

(1) *Myomas of the stomach*

Gastric myomas are far from rare (Golden and Stout, Muir, Ball). They are well circumscribed growths which project either into the stomach or into the peritoneal cavity. In the latter situation they often attain a great size. In 1930, I recorded a subserous gastric myoma which was known to have been present for at least 5 years and which finally weighed 900 grammes and there are many recorded instances of tumours far larger than this. Peptic ulceration of the overlying mucosa and often of the tumour itself is a frequent complication of intragastric growths. These may also cause partial invagination of the stomach wall or may cause ball valve obstruction of the pylorus. The smooth outlines of the filling defect seen in skiagrams following opaque meal may suggest a benign growth. Many instances of successful surgical removal have been reported. Though well defined to the naked eye the tumours are often not encapsulated but merge with the muscular coat of the surrounding stomach wall. Distinct regimentation of nuclei may be present and may cause confusion with neurilemmoma (see Golden and Stout). Indeed unless fixation has been

- Novak E (1941) *Gynecological and Obstetrical Pathology* Philadelphia
- Nygaard K K and Walters W (1937) *Arch Surg* 35, 1159
- Patch, F S and Rhea L J (1935) *Brit J Urol* 7 213
- ROSE, J D (1936) Myomata of the oesophagus *Brit J Surg* 24 297 (A good review)
- Schaper (1892) *Virchows Arch* 129 61
- Schmorl (1904) *Verh Dtsch path Ges* 8 80
- Schreiner B F (1929) *Surg Gyn Obst*, 48 730
- Seyler (1921) *Virchows Arch* 233 277
- SMITH, O N (1937) Leiomyoma of the small intestine *Amer J Med Sci* 194 700
(A brief but excellent outline with references)
- Steiner P E (1939) *Amer J Path* 15 89
- STOUT, A P (1937) Solitary cutaneous and subcutaneous leiomyoma *Amer J Cancer* 29 435 (A useful study and review)
- Stout A P (1938) *Amer J Cancer* 34 31
- Walter A (1929) *Z Geburts Gynak* 96 306
- Williamson H, and Brockman R St L (1928) *J Obst Gyn* 21 290
- Willis R A (1930) *Med J Austral*, 1 746
- Willis R A (1934) *The Spread of Tumours in the Human Body* London
- Willis R A (1941) *Med J Austral*, 11 258

(2) Solitary myomas

Solitary myomas of the skin or subcutaneous tissues have been less well recognized though they are probably as frequent as the multiple form. Stout has given a valuable review of these tumours.

(3) Sex

Multiple dermal myomas occur in males about twice as frequently as females, solitary myomas affect the sexes about equally.

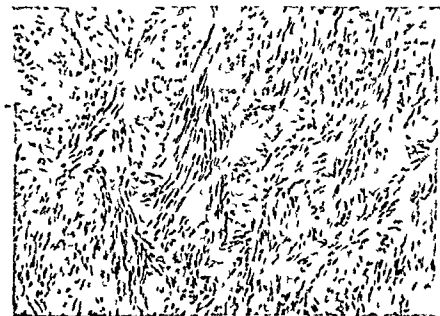


FIG. 361—Case VII. Well-differentiated myomatous structure in hepatic metastasis of leiomyosarcoma of rectum ($\times 150$).

(4) Age

In three quarters of the cases the multiple growths appear before the age of 30, less than one half of the solitary growths develop before 30 years. Many of the tumours are of slow growth and long duration.

(5) Site and origin

The commonest sites are the face, nipple area, extensor surfaces of the limbs and the external genitalia. Those situated in the dermis—and this applies to most of the multiple growths—clearly arise mainly from the *arrectores pilorum* muscles, while those of the subcutaneous tissue, usually solitary, more often take origin from the musculature of blood vessels. Other possible sources of tumours in particular situations are the non-striated muscles of the nipple and areola, scrotum and penis, labia and perianal region.

(6) Structure and growth

Dermal myomas, though often fairly well defined, are usually not encapsulated.

present, including renal cysts or hamartomas, cutaneous "adenomas", heterotopic islands of neuroglia in the meninges, malformations of the pancreas, of the heart itself, cleft palate, etc. Many cases are still born or die in infancy or childhood, but survival into adult life is possible, the oldest recorded patient being 35 years old (Steinbiss). The myocardial lesions show characteristic large vacuolated "spider" cells which contain abundant glycogen and often show radial or transverse striations of their peripheral cytoplasm. No instance of progressive growth has been reported, and the largest tumours rarely exceed 2 centimetres in diameter.

The pleomorphic celled growth described by Bradley and Maxwell as a "rhabdomyosarcoma" of the heart with metastases in lungs, liver and kidneys, is of doubtful nature, and no cross striations were found in the tumour cells. The nature of the tumour in a woman aged 37 reported by Larson and Sheppard as a "rhabdomyoma of the heart with sarcomatous extensions" is doubtful, insufficient details are given, and the transverse striations depicted might be artefacts and not true muscular striae. The spindle celled sarcoma of the heart reported by Muller (Case 4) as "probably an undifferentiated rhabdomyosarcoma" showed only 'a suggestion' of cross-striations in its cells.

RHABDOMYOSARCOMAS DERIVED FROM SKELETAL MUSCLES

The rarity of undoubted rhabdomyosarcomas of adult voluntary muscles is particularly noteworthy. The earlier literature (Benenati, Wolfensberger) contains many references to "rhabdomyosarcomas", but most of these were in the testis, kidney, uterus or other sites where teratomas or mixed tumours occur, and very few primary growths of skeletal muscles were recorded. Some of the more recently reported and acceptable cases may be briefly mentioned.

Wolbach (1928) described a rhabdomyosarcoma of the spinal muscles in a girl aged 4, and studied the mode of development of the cross striations in the tumour cells. Hirsch (1929) reported a tumour of the muscles of the leg in a boy aged 7, with metastases in many lymph glands, lungs and pelvic viscera, the cells contained abundant glycogen, and cross striated cells were present in the metastases. In a man aged 21, Hirsch (1931) also saw a huge tumour of the neck which he regarded as a mixed tumour of the thyroid containing striated muscle fibres, but, as the cervical muscles were extensively involved and as the supposed thyroid elements in the tumour were probably anaplastic sarcomatous tissue, the diagnosis of rhabdomyosarcoma of the muscles appears more probable. Cappell and Montgomery (1937) described two polypoid rhabdomyosarcomas of the palate, one in a girl aged 10 who died 7 years later with metastases in lungs and many lymph glands and the other in a girl aged 9 who died 6 years later with signs of pulmonary metastases. In these cases the polypoid masses clothed by intact epithelium, recalled the appearance of the grape-like sarcomas of the vagina in children. Two other cases of palatal rhabdomyosarcoma are referred to by Cappell and Montgomery, one reported by Nicory in a girl aged 5, the other by Martin and Alexander in a girl aged 6 who died later from recurrent growth and deposits in the cervical lymph glands. These palatal tumours presumably arise from the palatal muscles, though this has not been proved. A huge

CHAPTER 48

RHABDOMYOMA, RHABDOMYOSARCOMA AND RHABDOMYOBLASTIC MIXED TUMOURS

SEVERAL uncertainties combine to confuse discussion of tumours consisting of, or containing rhabdomyoblastic elements. Relatively rarely is the adult skeletal musculature of the body clearly and unmistakably the origin of a rhabdomyosarcoma. Most rhabdomyomatous tumours are either embryonic growths derived from immature myoblastic or undifferentiated mesenchymal tissue or mixed tumours in which other heterotopic tissues besides muscle are differentiated. Introduction of the term 'myoblastoma' has added to the confusion for its use is not uniform and it has often been applied far too uncritically. The so called 'rhabdomyomas' of the heart, with very rare and doubtful exceptions are not tumours at all but malformations.

A systematic account of rhabdomyoma is therefore impossible. I propose to deal with this heterogeneous group under the following headings:

- 1 Rhabdomyoma ' of the heart
- 2 Rhabdomyosarcomas derived from skeletal muscles
- 3 Myoblastomas '
- 4 The grape like vaginal sarcomas of children
- 5 Rhabdomyomatous tumours of the bladder
- 6 Rhabdomyomatous tumours of the male genitalia
- 7 Mixed mesenchymal tumours of the uterus
- 8 Rhabdomyomatous tumours of other parts
- 9 Rhabdomyoblastic tissue in embryonic renal and hepatic tumours and in teratomas
- 10 Rhabdomyomas in animals
- 11 General conclusions regarding the histogenesis of rhabdomyoblastic tissue in tumours

The discussion of 4 and 7 will involve consideration of the whole of these groups of tumours even though some of their members lack recognizable muscle for we cannot artificially divorce those in which myoblastic tissue has been demonstrated from those appearing to lack it. It is certainly a frequent, and sometimes a predominant, component of these tumours.

RHABDOMYOMA OF THE HEART

The so-called congenital rhabdomyomas of the heart well reviewed by Steinbiss, Farber and Labate can quickly be dismissed. They are not tumours but developmental anomalies. In most cases they are visibly multiple or accompanied by microscopic foci of similar malformed tissue in other parts of the heart as in Farber's case or the entire myocardium may be diffusely affected as in Schmincke's case. In many cases the patients are aments or epileptics with tuberosc sclerosis of the brain and other developmental anomalies also are often

striations can be found, the muscular nature of a tumour cannot be affirmed with certainty. I have examined many pleomorphic celled sarcomas involving muscles in adults, in the hope of being able to demonstrate their rhabdomyomatous nature, but so far in vain

h



FIG 364—(Dr L M Hawksley's specimen) Lingual myoblastoma from a man aged 60 showing preservation of general pattern of lingual musculature by the abnormal cells and the presence of Cohnheim's areas in some of them ($\times 200$)

As MacCallum pointed out, altered fibres of the invaded muscle may be mistaken for tumour cells. This source of error, of which some writers have been unaware, is excluded in MacCallum's specimens—rhabdomyosarcomas of the brachialis and gastrocnemius muscles in a man aged 59 and a woman aged 70—for mitoses were seen in striated tumour cells. Some of Rakov's figures of fibrils and cross striations are not wholly convincing, and, in any case, he gives

spindle celled sarcoma of the middle ear in a boy aged 5 described by Maconie was found by J Švejška to be a rhabdomyosarcoma (Fig 363) it may well have arisen from the palatal muscles around the Eustachian tube

The youth of the patients in all of the foregoing cases of rhabdomyosarcoma is noteworthy it raises the question whether the tumours arose from mature differentiated muscle fibres or from still immature embryonic myoblasts, a question all the more pertinent in view of the doubtful and limited capacity of striated



FIG 363—Rhabdomyosarcoma of middle-ear region in a boy aged 5 (*Maconie's case re investigated by Švejška* R C S Museum Accession No 296 iron haematoxylin stain) ($\times 800$)

muscle for proliferation once it has attained adulthood The resemblance of the palatal tumours to the vaginal ones both in gross and microscopic features including the presence of immature myxoma like tissue strengthens the idea that the former probably are as the latter certainly are (*see below*) truly embryonic tumours arising from young tissue which has never differentiated

On the other hand several workers (e.g. MacCallum Rakov) have shown that some pleomorphic-celled sarcomas in adults are rhabdomyosarcomas in which anaplasia has largely deprived the cells of striations and other distinctive structures Suggestive features are long strap-like cells with longitudinal fibrils which show up sharply in carefully differentiated iron haematoxylin preparations sharp zig zagging of these cells and fibrils and large rounded cells with one or several central nuclei and strongly eosinophil cytoplasm These features in a pleomorphic-celled sarcoma justify meticulous search for striae which may be found either as typical transverse striations in fusiform or strap like cells, or as regular beading of individual longitudinal fibrils or as radial striae or fine peripheral hatching in the large rounded eosinophil cells Unless distinct

plainly that the latter are not, as the name implies, immature cells undergoing differentiation but altered derivatives of the muscle fibres. True myoblasts in the embryo do not, at any stage, resemble Abrikossoff's "myoblasts", but similar appearances are seen in states of degeneration and regeneration of skeletal muscle following injury (see below).

Different usages of the name "myoblastoma" also cause confusion. Most writers have applied the term particularly to the benign lesions composed of large granular cells, but others have included also anaplastic malignant growths of supposed muscular origin. Thus Klemperer's first case was a pleomorphic celled sarcoma. Cappell and Montgomery's "myoblastomas" of the bladder and of

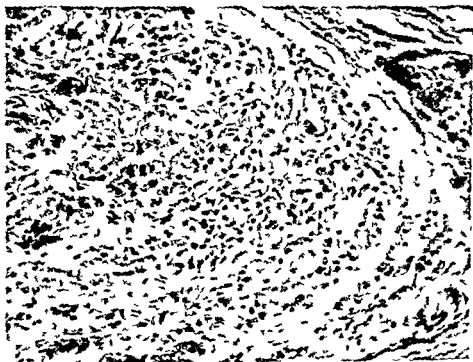


FIG. 366—(Colonel W. F. Harvey's specimen) Cutaneous myoblastoma of the knee region from a man aged 32. Tumour had been present 11 years, was 1.5 centimetres in diameter, was restricted to dermis and subcutis and unattached to muscle and had recently suffered slight superficial ulceration. ($\times 200$)

the spermatic cord were predominantly spindle-celled growths, and their "malignant myoblastoma" of the tongue was also an anaplastic spindle-celled sarcoma quite unlike the benign lingual "myoblastomas" of Abrikossoff.

Tumours dubbed "myoblastomas" in situations where no muscle is present of course cannot show transitions as conclusive evidence of their supposed muscular origin, and it is particularly significant that in none of them has unequivocal cross striation been observed, in striking contrast to their supposed counterparts on the tongue. What then is the evidence suggesting their muscular nature?

Clearly this—that they consist of cells more or less resembling the large granular striated cells of growths of known muscular origin. I agree with Gray (unawakened) that this resemblance however close does not prove identity. I have examined three growths from the skin of the thigh and one from the breast for structure identical with that depicted in "myoblastomas" (Fig. 366),

no details of the individual cases from which his figures came. It is significant that most of the indubitable rhabdomyosarcomas with beautifully striated cells have come from children or adolescents, and that such tumours are relatively very rare in adults. This fact should engender great caution in making a diagnosis of rhabdomyosarcoma in an adult, save on unimpeachable grounds.

MYOBLASTOMA

Under the title "Myoblastenmyome (later reduced to myoblastoma" by most writers) Abrikossoff (1926 and 1931) described peculiar growths of the tongue and other parts, consisting of large rounded ovoid or elongated cells with acidophil granular cytoplasm which in some tumours showed longitudinal and cross striations and transitions to undoubted muscle fibres but in other tumours showed no such evidence of their origin (Figs 364, 365). Although Abrikossoff

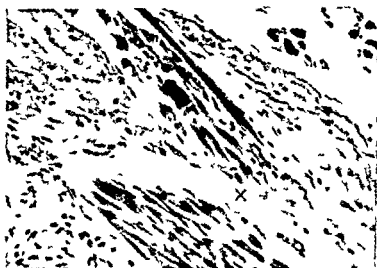


FIG 365 —Lingual myoblastoma from a boy aged 8. Transitions from normal to abnormal muscle fibres are visible at X ($\times 200$).

is credited with priority of recognition of a muscular origin of growths of this kind, a similar lingual tumour was clearly depicted and described as a "rhabdomyoma" by Keynes in 1926. Subsequent writers (Klemperer, Gray and Gruenfeld, Horn and Stout, Crane and Tremblay) added to the records of lingual "myoblastomas" and applied this name also to an increasing number of tumours in other situations including sites such as the skin and breast which normally contain no striated muscle, where it was assumed that the tumours arise from embryonal rests of aberrant myoblastic tissue (Horn and Stout).

(1) Possible fallacies regarding myoblastomas

Both the name "myoblastoma" and the identification of many of these growths as of muscular nature are open to serious question. Where, as in the tongue and occasionally elsewhere, the growth is undoubtedly muscular in origin, the transitional forms between striated muscle fibres and the myoblasts show

of normal looking fibres with swollen protoplasmic granular masses, transition forms between normal and granular cells and, in one specimen, gentle transition from the normal musculature to the altered tissue, the latter retaining the pattern of the former (See Figs 364, 365)

The fact that the tongue, an organ which is frequently and repeatedly subjected to small injuries, is by far the commonest site of these growths, suggests their traumatic origin, a suggestion strengthened by their regularly superficial situation on the dorsum or along the margins of the organ. Some of the extra lingual growths also have shown features strongly suggesting a traumatic or inflammatory



FIG 367—Irregular overgrowth of the epithelium overlying a lingual myoblastoma from same specimen as Fig 364 ($\times 60$)

origin e.g. the 'myoblastoma' of the thoracic wall reported by Grayzel and Friedman, a stony hard mass 2.7 centimetres in diameter, did not increase in size during the several months it had been noticed inflammatory leucocytes were present in it and the 'myoblasts' merged with well preserved muscle fibres.

One final feature of 'myoblastomas', which has some bearing on the present discussion is the frequent presence of irregular hyperplasia of the epithelium overlying them when they occur in the tongue or other immediately subepithelial sites. This hyperplasia, observed by most writers on the subject and depicted in Fig 367, may easily be mistaken for early invasive carcinoma. If 'myoblastoma

and in none of these could I see any reason—except cytological resemblance to the lingual growths—to suppose them to be of muscular nature. It has been admitted by several writers on the subject that they have confused xanthomatous collections of foam cells with myoblastomas" since which reporters of these growths have been careful to say that their 'myoblastoma' cells were not vacuolated but granular and that Sudan III and other fat stains gave negative results. Much has been made of the presence of glycogen in the large granular cells, but this finding is of little significance for real myoblasts may contain little or no glycogen, and other kinds of cells, including of course epithelial cells, may contain large quantities. I have not seen a specimen of congenital epulis or 'myoblastoma' of the gums of a new born infant, but from perusal of the several reports of this condition (Ceelen Meyer Crane and Tremblay) its muscular nature seems to me very dubious. Indeed, I am unconvinced of the muscular nature of any of the extra muscular 'myoblastomas' reported by Abrikossoff Ceelen Klemperer Horn and Stout and Crane and Tremblay who I think have fallen into the time honoured error of construing resemblance as identity. Some of these writers evidently harboured slight doubts of their own diagnoses witness the frequent use of such phrases as 'appear to be closely resemble' or "may be classified as myoblastoma".

(2) Neoplasia or regeneration ?

Returning now to the benign large granular celled myoblastomas of the tongue or of other skeletal muscular tissue in the lip cheek, limbs or elsewhere, there are strong grounds for doubting whether these are true neoplasms. In spite of the undifferentiated appearance of their cells and their not infrequent "infiltration" of adjacent tissues they are benign neither ulcerating metastasizing nor recurring after removal. The abnormal cells show no mitoses and the lesions usually remain quite small even after prolonged duration. Crane and Tremblay's tabular review shows many cases of lingual 'myoblastoma' which were only small nodules or 1 or 2 centimetres in diameter after several years duration—18 years in the case of Martinez. Of course small size and long duration do not exclude neoplasia but they certainly increase the suspicion that the lesions may be non neoplastic. Then many reporters of lingual lesions have seen clear transitions from normal skeletal muscle fibres to myoblasts muscle fibres often ending in bulbous granular swellings identical in appearance with the cells of the bulk of the lesion—an extraordinary relationship if this is indeed a neoplasm. And lastly, granular changes resembling those of 'myoblastomas' are sometimes seen in degenerative or regenerative lesions of striated muscle fibres. Thus Meyer depicted the typical appearance of myoblasts in damaged muscle fibres in an abdominal scar. Gray and Gruenfeld saw the same in association with an ulcer of the tongue and I have seen similar appearances in muscles after injury and after the application of radium. The varied appearances of degenerating muscle fibres following crushing injuries or ischaemic necrosis and of the regeneration sprouts which grow into the old sarcolemmal sheaths as depicted by Le Gros Clark are pertinent in this connexion.

I have examined 8 specimens of lingual myoblastoma all of which appeared to me clearly to be areas of altered muscle fibres. They often showed continuity

In the following case the tumour, though not polypoid or intra vaginal, contained rhabdomyomatous elements and almost certainly belonged to the group of tumours under discussion

Case II—History—After intermittent abdominal pain for 12 months a girl aged 6 years was admitted to hospital with a palpable large lower abdominal tumour. X ray irradiation failed to effect any improvement and she died 4 months later. *Necropsy*—A large lobulated growth filled the pelvis, compressed the intact bladder, uterus and vagina anteriorly and the rectum posteriorly and invaded the pelvic and iliac muscles but not the bones. Many pelvic and abdominal lymph glands contained large deposits of growth and there were scattered metastases in the peritoneum and in the lungs. *Histology*—Cellular sarcoma containing plump spindle cells, large irregular multinucleated cells with eosinophilic cytoplasm, many long cylindrical eosinophilic fibres closely resembling young skeletal muscle fibres with few faint striations discernible here and there and areas of oedematous or myxoma like tissue.

(1) Age

With rare exceptions, these tumours make their appearance before the age of 5 and in about one half of the cases before the age of 2. Dugge, however, refers to 2 reported cases in girls of 15 and 17 years.

(2) Site

Any part of the vaginal walls may be the starting point of the growths, but the most common site is the upper part of the anterior vaginal wall—20 of 33 cases in Adler's review. Occasionally the origin of the growth is close to the vulva, e.g. from the hymen in Amolsch's case. The base of the bladder is often implicated, and the tumour may project into it as well as into the vagina, as in my Case I.

(3) Appearance

'Botryoid' and "grape like" well describe the characteristic polypoid oedematous masses of growth which distend the vagina and project externally. The tumours also infiltrate the tissues of the pelvic floor and fill the pelvic cavity compressing the bladder anteriorly and the uterus usually laterally or posteriorly.

(4) Microscopic structure

This is fairly characteristic. The bulk of the growths usually consist of a mixture of oedematous or myxoma like tissue and more cellular spindle celled or pleomorphic celled sarcoma, scattered through which there may be a few or many cells with recognizable cross striations. Thorough search in well stained iron haematoxylin preparations may be necessary to discover them. Some tumours show no recognizable muscle elements appearing simply as embryonic cellular 'sarcomas'. The growth itself includes no epithelial elements, but the surfaces of the grape like masses are clothed by vaginal epithelium which dips down deeply into the intervening crevices of the tumour. The tumour and the overlying intact epithelium form an organized structure and gross ulceration is rare. Cartilage or bone has not been described in these growths though it is often present in the rather similar botryoid sarcoma of the cervix in adults (*see below*). Nagel reported a highly vascular 'angioblastic sarcoma' of the vagina of an infant which probably belongs in this group.

is indeed a neoplasm, this striking overgrowth of the epithelium is difficult to account for. But if it is a traumatic inflammatory or degenerative lesion concomitant irritative epithelial hyperplasia in the same area is readily understandable.

For the foregoing reasons, I join the considerable group of pathologists who doubt the neoplastic character of the benign 'myoblastomas' of the tongue and of other skeletal muscles. I believe these lesions to be the result of injury to muscle fibres with subsequent degenerative or regenerative changes. Large granular masses of sarcoplasm in visible continuity with residual muscle fibres strongly suggest regeneration sprouts comparable with those observed by Le Gros Clark in crushed muscle. Perhaps thermal or chemical injuries also may evoke the peculiar reactionary overgrowth seen in the so called 'myoblastomas'. Perhaps the granular 'myoblasts' include also in wandering macrophages, distended by glycogen and other products of the degenerating muscle fibres and assuming elongated forms within the sarcolemmal sheaths of the damaged fibres which they have invaded.

(3) Personal conclusions regarding 'myoblastomas'

- (i) The benign granular celled 'myoblastomas' of the tongue and of other skeletal muscular tissue are not tumours but degenerative or regenerative lesions of muscle fibres. If however the occasional existence of true neoplasms of this appearance were to be proved they should be called rhabdomyomas.
- (ii) Lesions of similar appearance in tissues where no striated muscle is present should not be called 'myoblastomas', their muscular nature is unproved.
- (iii) The term 'myoblastoma' is unnecessary for and should not be applied to, malignant tumours of proved muscular origin. These are rhabdomyosarcomas. If anaplasia deprives the cells of a rhabdomyosarcoma of the distinctive characters of striated muscle cells, especially cross striations, then certain histological recognition of the nature of the tumour becomes impossible. It is better frankly to recognize this difficulty than to take refuge in a name.
- (iv) The term 'myoblastoma' should therefore be discarded. It is only serving to perpetuate several erroneous or dubious concepts.

THE GRAPE LIKE SARCOMAS OF THE VAGINA IN CHILDREN

One of the earliest reports of these rare tumours was that of Marsh and Beck (1874). McFarland (1911) reviewed 32 of the earlier reports. Adler (1928) tabulated records of 41 cases in the German literature, and Dugge (1930) gave a good outline of the subject. In the following case the tumour though typical in other respects was predominantly vesico-urethral thus indicating the essential identity of this group of tumours and the vesical ones described below.

Case 1—History—A neglected child 2 years old with no available history was admitted to hospital because of a bulky polypoid growth protruding from the vagina. This progressed and the child died 2½ months later. *Necropsy*—The growth replaced the base of the bladder and urethra and protruded into the lower part of the vagina. The upper vagina and uterus were intact. *Histology*—Vascular undifferentiated spindle celled growth replaced the vesical and urethral mucosa and only slightly invaded the surrounding muscle. The surface of the polypoid protrusions was clothed by stratified epithelium.

A



B



C



FIG 368—Grape like rhabdomyosarcoma of bladder from a male child 18 months old. Longitudinal and cross striations were indefinite in ordinary preparations—those depicted here are from carefully differentiated iron haematoxylin stained sections. A and B = longitudinal fibrils with transverse striae. C = spherical cell with marginal radial striae giving rosette appearance and a neighbouring cell with fine marginal beading. (E Minchin's Case 1) ($\times 800$)

rhabdomyosarcoma with widespread metastases in a man aged 26. Khoury and Speer tabulated 18 reported cases of rhabdomyosarcoma of the prostate, 12 of whom were children or young adults. (See also Fig 369). The youth of these

(5) Metastases

Metastases have seldom been recorded. In a few cases deposits in regional lymph glands are mentioned, and in Dugge's case there were some small metastases also in the lungs. Nagel's case of highly vascular tumour showed invasion of the spinal canal and of the iliac vein and inferior vena cava and multiple tumour emboli and metastases in the lungs. My Case II above showed lymph nodal, peritoneal and pulmonary metastases.

RHABDOMYOMATOUS TUMOURS OF THE BLADDER

Early records of tumours of this kind (cited by Monckeberg and Houette) were those of Cattani, Vincenti and Huser from boys of 12, 13 and 7 years respectively. Pavone's specimen from a woman aged 22, and Monckeberg's own specimen from a woman aged 23. In this last case however, although the tumour cells resembled skeletal muscle fibres in other respects indubitable cross striations were not found and this applied also to two cases described by Cappell and Montgomery. Shattock reported four specimens of vesical rhabdomyoma all from children three boys and a girl. In all cases the tumours formed multiple sessile or pedunculated mucosal polypi clothed by epithelium involving the lower half or two thirds of the organ. In one of the boys growths were present also in the mucosa of the prostatic urethra and in the female case (one of John Hunter's original specimens, still preserved in the Museum of the Royal College of Surgeons, London) the tumours projected into the urethra. Houette gave a good description of a congenital rhabdomyoma of the bladder which showed great cellular pleomorphism and the differentiation of striated muscle fibres from undifferentiated cellular tissue. White briefly reported a myxoma like rhabdomyosarcoma from the bladder of an infant aged 20 months. The tumour in Cattani's case also was myxomatous in appearance. Hirsch and Gasser reported a rhabdomyosarcoma of the neck of the bladder in a boy aged 5 and Khoury and Speer saw a similar growth which involved also the prostate and urethra in a male infant who had had symptoms since birth. (See also Fig 368.)

It must be mentioned in parenthesis here that cartilage containing or bone containing tumours of the bladder like those described by Wright Smith and Pollack are probably unrelated to the rhabdomyomas. Nor need they be regarded as these writers have regarded them as teratomas. They are sarcomas or carcinomas with stromal metaplasia perhaps induced by the neighbouring vesical epithelium.

RHABDOMYOSARCOMAS OF THE MALE GENITALIA

(1) Rhabdomyosarcomas of the prostate

Of 82 reported prostatic sarcomas reviewed by Smith and Torgerson while those in adults were very heterogeneous and many of them of doubtful nature 25 of them were from children in the first decade and many of these were recorded as either myxosarcomas or rhabdomyosarcomas. All 6 rhabdomyosarcomas including Kaufmann's 3 examples were from young subjects their ages ranging from 9 months to 31 years. Additional reports include that of Wachs of a congenital rhabdomyosarcoma and that of Foucar of 1

tissue which replaced the endometrium from fundus to cervix but did not extend into the myometrium, microscopically this was found to be typical astrocytic neuroglial tissue with characteristic staining properties, the only other foreign tissue found was one small nodule of cartilage. Orsos discussed whether the condition arose from implanted embryo tissue, from the sympathetic nerves of the uterus, or from a teratoma, and he inclined to the first view. In any case, the lesion was clearly a peculiar one and not to be included amongst the mesenchymal mixed tumours.

- (f) *Epithelial tissues* in these growths have usually been regarded as only included endometrial or cervical epithelium, and not intrinsic constituents of the tumour tissue. Non-ulcerated botryoid growths have a complete epithelial investment, and, as in the similar vaginal tumours of children the epithelium may dip deeply into the tumours between adjacent polypi. While it seems clear that the non epithelial tissues form the essential and bulkiest part of these growths, the abundance of endometrial or cervical glandular tissue in some of them at least shows great concomitant hyperplasia if not neoplasia. Rarely, as in Nicholson's case, the uterine epithelium is simultaneously cancerous intimately admixed with the mesenchymal elements and appearing with them in metastases. My Case IV of Chapter 31 afforded an example of an endometrial mixed tumour containing both epithelial and non epithelial elements.

(5) Histogenesis

Many workers have followed Wilms in supposing the uterine mixed tumours to arise from developmentally misplaced tissues. This view should be discarded. It is discredited by the researches of experimental embryologists, and it is as unnecessary as it is improbable. The supposition that undifferentiated "rests" of developmentally heterotopic tissues may remain in the endometrium for the whole of a woman's reproductive life, surviving multiple pregnancies, and eventually producing a mixed embryonic tumour at the age of 50 or 60 or 70 is absurd. Pfannenstiel in his original account in 1892 suggested that these growths arose from the endometrial stroma and that the several heterotopic tissues developed by aberrant differentiation or metaplasia. Nicholson supported this view: "the tumours can be explained on the assumption of a process of de-differentiation and rejuvenescence of the stroma of the uterine mucosa". I, too, hold this opinion. The endometrial stroma is a peculiar and highly labile tissue. Why should it not possess wide potencies for aberrant differentiation? Indeed we need assume but little more lability in this respect than we already know obtains for this and other tissues of mesenchymal origin. The metaplastic formation of mucoid tissue, cartilage and bone is a commonplace event in many parts of the body including the endometrium in non neoplastic states (Gierke). The presence of adipose tissue in a mixed tumour of the uterus no more presupposes a dislocated "rest" than it does in a uterine myoma. Muscular tissue, especially striated muscle is the only ingredient of mixed tumours that need excite any wonder or call for any special hypothesis regarding histogenesis. The development of muscle by aberrant differentiation in a plastic mesenchymal tumour tissue which has displayed its plasticity by producing also cartilage, bone and adipose tissue, is a much more probable event than the life long retention of rests

patients the frequent presence of undifferentiated mesenchyme like tissue as well as muscular elements in the growths, and the homology of the upper vaginal and prostatic regions together suggest that the prostatic sarcomas of children and young adults are comparable with the vaginal and cervical sarcomas of children. Perhaps the embryonic mesenchyme around the upper part of the urogenital sinus is in both sexes prone to the development of embryonic tumours. It is therefore uncertain whether the prostatic rhabdomyosarcomas take origin from

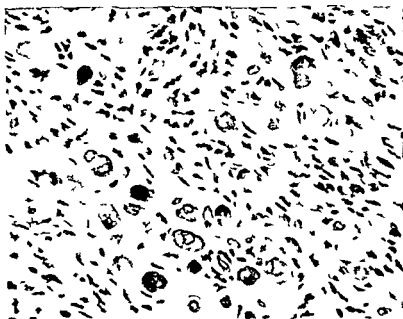


FIG. 369—Large rounded strongly eosinophil faintly striated cells in a rhabdomyosarcoma of the prostate from an infant 9 months old (*E. Munchin's Case II*) ($\times 350$)

this mesenchyme in its immature stage or from the striated muscle fibres which are present in the capsule of the prostate and are sometimes found also even in the periphery of the gland itself.

(2) Rhabdomyosarcomas of the spermatic cord and epididymis

Hirsch (1934) reviewed 12 previous reports of rhabdomyosarcomas of the cord or epididymis in several of which however the tumours involved the testis so that the possibility of them having been testicular teratomas cannot be altogether excluded. Of the 12 tumours 10 were from minors including 5 children aged 5 years or under—in the youngest patient the tumour had been noticed at the age of 10 months. In Hirsch's own case the boy was 16 years of age and the tumour occupied the epididymis but was separate from the testis. Again the youth of the victims of these tumours suggests an origin during early development and it remains doubtful whether the rhabdymatous tissue arises from the actual

all rather diagrammatic drawings. In a subject of unspecified age Gowers saw a mass of adipose tissue containing scattered striated muscle fibres, which enveloped the nerves of the cauda equina.

RHABDOMYOBLASTIC TISSUE IN TERATOMAS AND IN EMBRYONIC RENAL AND HEPATIC TUMOURS

This need only be mentioned here, details are given in the appropriate chapters. In the present connexion the occurrence of striated muscle in these growths is important in two respects, (a) because occasionally it is an abundant and conspicuous component, witness the fact that during the last century not a few of the teratomas of the testis and embryonic tumours of the kidney were called 'rhabdomyosarcomas', and (b) because it shows that rhabdomyoblasts can develop by aberrant differentiation in neoplastic embryonic tissues.

RHABDOMYOMATOUS TUMOURS IN ANIMALS

(1) Multiple "rhabdomyomas" of the heart

Multiple "rhabdomyomas" of the heart have been seen in young pigs (references by Farber and Feldman), and in a guinea pig (Hueper).

(2) Rhabdomyomatous tumours of skeletal muscles

These have been found in several species of fish (references by Nicory Haddow and Blake Kolmer). Feldman described and depicted two good examples from mammals, one from the leg of a 5 year old horse and the other from the pre scapular region of a year old sheep. He referred also to the scanty previous reports of rhabdomyomas of skeletal muscles in animals, including horse, ox and chicken.

(3) Rhabdomyomatous tumours in other sites

Feldman redescribes and depicts a remarkable specimen recorded by Day, one of multiple growths consisting of abundant striated muscular tissue along with scattered glandular elements in the lungs of a 5 month-old lamb. Other organs were said to be normal but the possibility remains that the growths may have been metastases from an undiscovered primary growth e.g. in the testis. If they were indeed primary in the lung, they were comparable with those in Zipkin's case already referred to. Feldman also mentions a rhabdomyoma of the vagus nerve seen by Gratia in an old horse but no details are available.

GENERAL CONCLUSIONS REGARDING THE HISTOGENESIS OF RHABDOMYOMAS

Several facts suggest that most rhabdomyomas are embryonic growths arising from immature myoblastic tissue and not from already matured striated muscle fibres. These facts are

(1) Age incidence

With the exception of the uterine mixed tumours nearly all unquestionable rhabdomyomatous growths arise early in life. Most of the unequivocal rhabdomyosarcomas of skeletal muscles have been in children or adolescents, all of the

of embryonic tissue of multiple kinds. Case IV of Chapter 31 showed plainly the development of abundant smooth muscle from the endometrial stroma.

Indeed we can go further. The relationships and transitions of the different tissues seen in the mixed tumours show clearly that these do not arise as separate elements which then mix together, but that they are each and all products of the undifferentiated mesenchymal cellular myxosarcoma like tissue which is invariably present. This is the essential parenchyma of the tumours from which all the differentiated elements arise, it is neoplastic endometrial stroma which in the process of becoming neoplastic has again become embryonic and has re-acquired unusual potencies for aberrant differentiation.

(6) Growth and behaviour

Both the corporeal and cervical mixed tumours are highly malignant, frequently recurring or metastasizing, and this in spite of the fact that they often appear confined to the uterus when first seen. Recurrence or local metastasis is frequent in the pelvic cavity or peritoneum, perhaps ligature of the tubes before performing hysterectomy and care not to spill loose particles of growth during its performance might minimize this risk. Remote metastases are usually situated in the lungs but may occur in other parts too, e.g. the kidneys and bones in Duggan's case. Their structure is usually cellular and anaplastic, but careful studies of further necropsy cases is necessary to determine whether all the potencies of the tumour tissue for divergent differentiation may reappear in metastases.

RHABDOMYOMATOUS TUMOURS OF OTHER PARTS

Very rarely a rhabdomyoma or rhabdomyosarcoma of some other viscus is reported. This may be in an organ where striated muscle is present as in Wolfenberger's case of rhabdomyosarcoma of the oesophagus, or it may be in a part where normally there is no striated muscle. Thus Helbing described a rhabdomyoma replacing the lung of a man aged 23, and Zipkin described a similar growth in the lung of a 33 weeks foetus in which bronchi traversing the striated muscular tissue themselves had striated instead of smooth muscle in their walls. In both of these cases the lesion was probably a malformation rather than a true tumour, but in a man aged 52 McDonald and Heather saw a pulmonary rhabdomyosarcoma with massive polypoid extensions through the pulmonary veins into the left atrium. Needless to say in such a case as this great care must be taken (a) to exclude the possibility of the growth being a teratoma with plentiful muscular elements (b) to exclude the possibility of it being a metastasis, e.g. from a small testicular tumour, and (c) that the cross striations are genuine ones and not merely artefacts produced by shrinkage, fragmentation or concertina-like buckling of cells. In a negress aged 38 Sailer saw a pleomorphic celled rhabdomyosarcoma of the breast with distinctly cross striated cells in the pulmonary metastases. The cross striations in the rhabdomyoblastic cells seen by Govan in two mixed tumours of the breast were less distinct, being restricted to beaded cell margins. Masson and Martin reported rhabdomyosarcomas of peripheral nerves in three young subjects with neurofibromatosis. It is regrettable that the micro figures depicting these extraordinary tumours are

have concluded that they display divergent differentiation of pluripotential cells derived from the uterine stroma. Since neoplastic uterine stroma can produce rhabdomyoblasts in the adult, the possibility that other adult tissues may be capable of doing the same cannot be excluded. However, for reasons already given, it is probable that very few, if any, of the extra-uterine rhabdomyomatous tumours arise in this way, the origin of most of them from young still undifferentiated tissue seems certain.

REFERENCES

- Abrikossoff A (1926 and 1931) *Virchows Arch*, 1926 260 215 and 1931, 280 723
 Adler K (1928) *Arch Gynak* 133 100
 Amolsch A L (1939) *Amer J Cancer* 37 435
 Benenati U (1903) *Virchows Arch* 171 418
 Bradley E B and Maxwell E S (1928) *J Amer Med Assoc* 91 1352
 CAPPELL D F, and MONTGOMERY, G L (1937) On rhabdomyoma and myoblastoma, *J Path Bact* 44 517 (A valuable account of several certain and some presumed rhabdomyoblastic tumours)
 Ceelen W (1931) *Virchows Arch* 280 741
 CLARK, W E Le Gros (1946) An experimental study of the regeneration of mammalian striped muscle *J Anat* 80 24
 Crane A R and Tremblay R G (1945) *Amer J Path* 21, 357
 Duggan A R H (1939) *Med J Austral* 1 612
 Dugge M (1930) *Virchows Arch* 277 1
 Ehrlich H E (1942) *Amer J Obst Gyn* 43 1021
 FARBBER, S (1931) Congenital rhabdomyoma of the heart *Amer J Path* 7 105 (A useful review)
 Feldman W H (1932) *Neoplasms of Domesticated Animals* Chapter X Philadelphia
 Foucar F H (1935) *Amer J Path* 11 753
 Gierke E (1935) *Zbl allgem Path* 62 145
 Govan A D T (1945) *J Path Bact* 57 397
 Gowers W R (1876) *Trans Path Soc Lond* 27 19
 GRAY S H and GRUENFELD, G E (1937) Myoblastoma *Amer J Cancer*, 30 699 (A useful critical review)
 Grayzel D M and Friedman H H (1941) *Arch Path* 31, 512
 Gunning R E L and Ross C A (1940) *Surg Gyn Obst* 70 230
 Haddow A and Blake I (1933) *J Path Bact* 36 41
 Harding W G and Hankins F D (1933) *Arch Path* 16 480
 Helbing C (1898) *Zbl allgem Path* 9 433
 Hirsch E F (1929) *Arch Path* 8 9
 Hirsch E F (1931 and 1934) *Amer J Cancer* 1931 15 55 and 1934 20 398
 Hirsch E F and Gasser G W (1944) *J Urol* 51 517
 Horn R C and Stout A P (1943) *Surg Gyn Obst* 76 315
 HOUETTE C (1929) Rhabdomyome diverticulaire congenital de la vessie, *Ann d Anat path* 6 267 (A good account with full reference list on rhabdomyoma)
 Hueper W C (1940) *Amer J Path* 17 121
 Kaufmann E (1902) *Dtsch Chir* 53 381
 Keynes G (1926) *Brit J Surg* 13 570
 Khoury E N and Speer F D (1944) *J Urol* 51 505
 Klemperer P (1934) *Amer J Cancer* 20 324
 Kolmer W (1928) *Virchows Arch* 268 574
 Labate J S (1939) *Amer J Path* 15 137
 Larsen C P and Sheppard J A (1938) *Arch Path* 26 717
 Liebow A A and Tennant R (1941) *Amer J Path* 17 1
 Lochrane C D (1933) *Proc Roy Soc Med* 26 1429
 Macone A C (1944) *J Laryng Otol* 59 32
 MacCallum P (1933) *Austral NZ J Surg* 2 296

palatal tumours reported have been in children, the rhabdomyosarcomas of the vagina are almost restricted to early childhood most of those of the prostate and those of the spermatic cord and epididymis occur in children or adolescents, and so do those of the bladder. Yet the occasional occurrence of pleomorphic called sarcoma of skeletal muscles in adults with definite striation of their cells makes it impossible to deny that matured muscle fibres may sometimes give origin to tumours. It must be repeated however that anaplastic tumour cells lacking cross striations cannot be identified with certainty as rhabdomyomatous and that most sarcomas in which undoubted cross striations are demonstrable are from youthful subjects.

(2) Structure

Many rhabdomyosarcomas especially those in young children contain undifferentiated myxoma like tissue closely resembling embryonic mesenchyme. This applies particularly to the palatal vaginal and prostatic tumours the structure of which leaves little room for doubt of their truly embryonic nature. In these sites there occur also similar tumours devoid of recognizable muscle elements and composed solely of myxosarcomatous or embryonic mesenchymal tissue.

(3) Sites of origin

It is a striking fact that in spite of the vast bulk of the skeletal muscles of the body undoubted rhabdomyomatous tumours are much rarer in this than in certain special situations where normally no striated muscle is present or where the scanty muscle which is present is only doubtfully the real source of the tumours—vagina, prostate bladder spermatic cord palate. It is of course possible that the palatal tumours spring from the palatal muscles the prostatic tumours from the stray striated fibres found in the capsule of this organ and the vaginal tumours from outlying strands of the vaginal or external vesical sphincters. But even so how remarkable that these scraps of muscle should produce far more tumours than all the rest of the voluntary musculature!

From these three sets of facts it seems clear that the usual source of rhabdomyomatous tumours is not adult muscular tissue but embryonic tissue either immature prospective muscular tissue or indifferent mesenchymal tissue with the potency for aberrant differentiation of muscle fibres. That mesenchymal tissues not of rhabdomyoblastic origin can at times undergo such aberrant differentiation is proved by the occasional presence of striated muscle in unusual sites such as the bronchi uterus ureter or spinal theca by its development in embryonic renal and hepatic tumours and by its frequent presence in mixed tumours of the uterus. These pathological facts show plainly that the capacity to form striated muscle fibres is not restricted to cells derived from the embryonic myotomes but that under appropriate circumstances it appears also in plastic mesenchymal cells of other origins.

The implications already touched on of the development of rhabdomyoblasts in the mixed tumours of the uterus deserve further emphasis. Not only does this show that mesenchymal cells of non muscular origin can re-differentiate into myoblasts but also that this change can take place in adult tissue. We have rejected the view that the uterine mixed tumours arise from embryonic rests and

CHAPTER 49

THE TUMOURS OF LYMPHOID TISSUE

NOWHERE in pathology has a chaos of names so clouded clear concepts as in the subject of lymphoid tumours. Lymphoma, lymphocytoma, lymphosarcoma, lymphoblastoma, follicular lymphadenopathy, lymphatic leukaemia, lymphoid leucosis, leukaemic and aleukaemic lymphadenosis, Hodgkin's disease, Hodgkin's sarcoma, lymphadenoma, lymphogranuloma, leucosarcoma, pseudoleukaemia, endothelioma, reticulosarcoma, reticulosis, reticulo endotheliosis, mycosis fungoides—these are some of the names which have been applied to neoplasms of lymphoid tissue and often applied in different senses by different writers. As in so many other fields of pathology, this confusion has resulted largely from failure to recognize frankly certain intrinsic difficulties in the subject and to apply certain general principles in their elucidation. What are these difficulties and these principles?

FACTORS CONFUSING THE NOMENCLATURE OF LYMPHOID TUMOURS

(1) Confusion regarding the histogenesis and relationships of the components of lymphoid tissue

A great deal of the redundant nomenclature has come from too rigid concepts of the specificity of the several differentiated constituents of lymphoid tissue. As long as one believes that lymphoblasts, reticular cells, endothelial cells and fibroblasts in this tissue are immutable and distinct species of cells, so long will one imagine corresponding distinctions to exist between the variant types of lymphoid tumours. Informed study of the lymphoid tumours, however, should soon convince the unbiased that the components of lymphoid tissue—lymphocytes and reticulo endothelial framework alike—are derived by divergent differentiation from primitive mesenchymal stem cells. The combinations and transformations seen in tumours show clearly that many of them have arisen from and consist of plastic bipotential tissue capable of such divergent differentiation. Recognition of this will enable us to see the several named types of tumours not as rigidly distinct species but as related variants of a single species and the names we apply will then be used as convenient descriptive labels and not as bones of contention over histogenesis. We will cease to be surprised that Hodgkin's disease merges with lymphosarcoma on the one hand and with 'reticulosarcoma' on the other.

This is the place also to deprecate too great a reliance on supposedly specific reticulin stains. 'Reticulin' is not a specific substance but only a form of collagen found in particular situations and not to be sharply distinguished from ordinary connective tissue fibres either structurally or tinctorially. The distribution and staining properties of collagenous tissues—including 'reticular tissue'—in tumours and inflammatory lesions are infinitely variable. My opinion after a considerable experience of special stains for connective tissue and reticulin is that while these often do delineate fairly characteristic patterns in typical specimens of particular classes of tumours, they are of no value in identifying

- McDonald S and Heather J C (1939) *J Path Bact* 48 533
- McFarland J (1911) *Amer J Med Sci* 141 570
- Marsh H and Beck M (1874) *Trans Path Soc Lond* 25 178
- Martin G E and Alexander W A (1924) *J Laryng Otol* 39 312
- Masson P and Martin J F (1938) *Bull Assoc franç Cancer* 27 751
- MEIKLE G J (1936) Mesodermal mixed tumours of the uterus *J Obst Gyn* 43 821
(A good review)
- Meyer R (1932) *Virchows Arch* 287 55
- Minchin E (1947) *Brit Med J*, II 94
- Monckeberg J G (1907) *Virchows Arch* 187 471
- Muller W (1932) *Virchows Arch* 284 105
- Nagel W (1933) *Zbl allgem Path* 59 129
- NICHOLSON, G W (1918) Multiple mesodermal mixed tumours of the uterus associated with pluricentric carcinomata *Guy's Hosp Rep* 69 173 (An excellent account of a remarkable specimen)
- Nicory C (1923) *Brit J Surg* 11 218
- Orsós F (1933) *Z Geburts Gynak* 107 384
- Pfannenstiel J (1892) *Virchows Arch* 127 305
- Pollack A D (1936) *Amer J Path* 12 561
- Rakov A I (1937) *Amer J Cancer* 30 455
- Sailer S (1937) *Amer J Cancer* 31 183
- Schminke A (1922) *Beitr path Anat* 70 513
- SHATTOCK, S G (1909) Rhabdomyoma of the urinary bladder *Proc Roy Soc Med* 3 Path Sec 31 (An important record of 4 specimens)
- SHAW, W (1928) Mixed tumours of the uterus and vagina *J Obst Gyn* 35 498 (The best general account of the subject)
- Smith R R and Torgerson W R (1926) *Surg Gyn Obst* 43 328
- Steinbiss W (1923) *Virchows Arch* 243 22.
- Wachs E (1937) *Zbl Chir* 64 1352
- White H P W (1929) *Proc Roy Soc Med* 22 1382
- Wolbach S B (1928) *Arch Path* 5 775
- Wolfe S A (1932) *Amer J Obst Gyn* 23 232
- Wolfensberger R (1894) *Beitr path Anat* 15 491
- Wright Smith R J (1929) *Austral NZ J Surg* 2 271
- Zipkin R (1907) *Virchows Arch*, 187, 244

(4) Practical difficulties of micro-diagnosis of early neoplastic changes in lymphoid tissue

The micro-diagnostician has no greater bane than the 'doubtful lymph gland'. Early lymphosarcomas, early Hodgkin's disease, mild inflammatory reactions and reticular hyperplasias may be difficult or impossible to distinguish from one another. This is not surprising, for lymphoid tissue varies greatly in structure in its normal or mildly hyperplastic states, its reticulo-endothelial cells proliferate quickly and in diverse ways in response to slight irritants, and many of the lymphoid tumours even when well established mingle intimately with the residual normal tissues. Let us frankly recognize our liability to err here, while striving to learn as much as possible by careful follow-up of all doubtful cases. No pathologist lives long enough to become infallible in this field.

THE HISTOGENETIC KINSHIP OF THE LYMPHOID TUMOURS

Ginsburg has given a good historical summary of the controversy over the relationship of lymphosarcoma and Hodgkin's disease, how at the end of the last century, Kundrat, Paltauf, Sternberg and others attempted sharp distinction of the two and how Gibbons, Mallory, Warthin and others later insisted, on the contrary, that they were closely related. Mallory (1914) went even further and boldly declared lymphosarcoma, lymphatic leukaemia and Hodgkin's disease to be only variants of one kind of tumour, 'malignant lymphoblastoma'. Most pathologists and all clinicians, however, continued—and many still continue—to think of these three conditions as distinct and to argue about their relationships.

In 1931, Warthin published a succinct and important paper in which he concluded 'that Hodgkin's disease is a neoplasm and related genetically to the lymphoblastomas, of which both the aleukaemic and leukaemic forms are identical pathologically, and that mycosis fungoides is likewise a neoplasm belonging to the same generic group. The essential differences between these different clinical forms consist in different degrees of differentiation or entodifferentiation, and the organ or tissue primarily involved. Transition forms exist between all of these groups, and one type may be transformed into another'. Most recent students of the subject, including myself, have reached substantially the same conclusions as Warthin, and have included the relatively rare reticulosarcomas and follicular lymphomas in the same family, at opposite ends of the scale as regards malignancy. The whole group is thus seen as an entity 'sarcomas of lymphoid tissue', within which a wide range of structure and behaviour justify, for descriptive and clinical purposes, the use of special names for the main variants. But these variants are not distinct species of growths. (See Dawson *et al*, Warren and Picena, Gall and Mallory Herbut *et al*.)

Complicated pigeon-hole systems of clinical classification of the variants of lymphoid and other haemopoietic tumours, like those of Callender and of Forkner, are to be avoided, because they create a multiplicity of names which then falsely assume the status of entities, even against their creators' intentions. The same applies to complicated histopathological subdivisions, like that of Robb Smith, which, praiseworthy though it may be as an attempt to clarify a confused subject, obscures the essential unity of the whole group of lymphoid neoplasms. Many of

tumours of unusual structure or uncertain nature. In my hands 'reticulin' stains have rarely if ever given any useful information which was not equally well obtained by the more usual staining methods. To depend on 'reticulin' staining for the sub-division of lymphoid tumours or to distinguish these from diffusely infiltrating secondary tumours in lymphoid tissue is to set up purely artificial distinctions and to add to the confusion.

(2) Multiple names due to differences of cellular maturity or anaplasia in tumours

Further artificial distinctions are created by naming tumours merely according to the degree of differentiation attained by their cells. Thus a tumour composed of highly differentiated lymphoid tissue with follicles is 'giant follicular lymphadenopathy'—one composed mainly of well differentiated lymphocytes but without follicular arrangement is 'lymphocytoma'—one composed mainly of immature lymphocytes is 'lymphoblastoma'—one composed of undifferentiated mesenchymal stem cells is 'syncytial reticulosarcoma'. Yet all of these are histogenetically identical growths differing only in their rates of growth and therefore the degrees of differentiation towards that of lymphoid tissue which they attain. They are all 'lymphosarcomas', in that they are malignant mesenchymal tumours with a tendency to differentiate into lymphocytes. To give different members of the group different names merely because of their differing degrees of cellular anaplasia or maturity is as if one were to attempt to sub-divide skin carcinomas into 'epidermocytomas', 'epidermoblastomas' and 'primitive epithelioblastomas' according to their degree of differentiation.

A further feature related to the cellular maturity of lymphoid tumours complicates nomenclature—that is the presence or absence of a leukaemic blood picture. It cannot be too strongly insisted that lymphoid leukaemia and lymphosarcoma differ only in the quite incidental circumstance of whether or not the malignant lymphocytes enter the circulating blood in demonstrable numbers. Leukaemia is merely an inconstant concomitant of lymphosarcoma of interest to the haematologist but of no significance in fundamental classification and nomenclature of lymphoid tumours. Once this essential fact is admitted names such as 'pseudo leukaemia', 'aleukaemic leukaemia', 'leucosis' and 'leucosarcoma' will cease to cause perplexity and will have only an antique interest.

(3) Confusion due to mistaking secondary tumours in lymph nodes for primary ones

This has been a serious source of error in the description and naming of primary lymphoid tumours. Metastatic deposits in lymph glands from unsuspected primary carcinomas have frequently been mistaken for 'endotheliomas', 'reticulocytomas' and other primary lymph glandular tumours. In 1934 I gave instances of such mistakes and rejected many earlier reports of 'endothelioma' on this ground. It is to be insisted that when confronted with a lymph nodal tumour the structure of which perplexes and elicits differences of opinion from experienced pathologists, no final diagnosis should be made until careful necropsy has excluded the possibility of it being a metastatic growth. To accept it as primary and to force it into one or another of our preconceived sub-groups is to commit an error more often than not and so to perpetuate misconceptions of the structure possible within those sub-groups.

often leading ultimately to widespread disease of many lymph nodes with or without involvement of the spleen, and sometimes associated with areas of Hodgkin's structure or terminating in more active sarcomatous growth or leukaemia. The affected glands show abundant well differentiated large follicles with germinal centres, but sometimes with more active diffusely cellular areas like ordinary lymphosarcoma. The disease is to be regarded as a slowly progressive highly differentiated form of lymphosarcomatosis. The average total duration of Gall and Mullory's 38 cases was 5.6 years, a longer mean duration than for any other type of malignant lymphoid tumour, more than half the cases survived 5 years and 16 per cent survived 10 years. Males and females were in equal numbers. For the following example of the disease, I am indebted to Dr C. A. Duncan of Hobart, Tasmania.



FIG 371—Case II Follicular lymphosarcoma ($\times 40$)

Case II—History—A man aged 46 had first noticed enlargement of lymph glands 8 years previously. These had slowly increased but general health had remained good. Some cough and pain in the chest had developed recently. Examination showed cervical axillary, iliac and inguinal glands all greatly enlarged, some measuring 7 centimetres in diameter, discrete, hard and mobile, also moderate firm splenomegaly. Blood examination showed a few nucleated red corpuscles but no other changes. Leucocyte count was 8,000. Clinical diagnosis, Hodgkin's disease. A lymph gland 3 centimetres in diameter, firm and well-encapsulated, was excised for examination. Patient died 4 months later. *Histology*—Well differentiated lymphoid tissue with many large follicles but with some diffuse areas, and less regular architecture than that of Case I (Fig. 371).

LYMPHOSARCOMA AND LYMPHOCYTIC LEUKAEMIA

Lymphosarcoma means a malignant tumour of lymphoid tissue which is predominantly lymphocytic or lymphoblastic in structure. It includes both lymphocytomas and 'lymphoblastomas', the distinction between which is entirely arbitrary and depends only on the degree of differentiation of the malignant lymphoid cells. Moreover, the least differentiated lymphosarcomas merge

the variants of structure given different names by Robb Smith may be seen in one tumour. What is wanted is not more, but less complexity in our histogenetic concepts. The structural plasticity of lymphoid tissue and its tumours demands the simplest possible nomenclature and avoidance of needless arbitrary distinctions.

However, this essential unity of the whole group of primary lymphoid tumours does not call for abolition of broad sub grouping according to the structure and behaviour of its main variants. The sub grouping will continue to have clinical and descriptive value, but it must not cause us to forget the kinship of the sub-groups and the existence of tumours of intermediate form between them. We will briefly consider the following sub-groups:

- (a) Follicular lymphoma
- (b) Lymphosarcoma with or without leukaemia,
- (c) Hodgkin's disease,
- (d) Reticulum cell sarcoma

It must be clearly understood that these are main groups only and that while many tumours fall into one or other of them, others show all possible combinations and transitions. These combinations and transitions will cause us perplexity only if we allow the names of our four main sub groups to assume the status of distinct species.

FOLLICULAR LYMPHOMA

Follicular lymphoma means literally a lymphoid tumour in which differentiation of follicles takes place. In this sense there are two rather distinct groups of cases, both of which are rare—(a) a localized benign lymphoma and (b) a multiple malignant form with or without splenomegaly.

(a) Localized benign lymphoma

This occurs as a slow enlargement, often over a period of several years, of a single lymph gland, usually in the neck, and usually in a middle aged or old person. The excised gland, which may have attained a size of 5 centimetres or more in diameter, is ovoid, smoothly encapsulated, and on section shows uniform firm, but not hard, white tissue in which lymphoid nodules may be discernible by the naked eye. Microscopical examination confirms that the structure is that of well-differentiated lymphoid tissue in which large follicles with prominent germinal centres are scattered throughout. While extension to other glands or more active sarcomatous growth or leukaemia may eventually supervene, not a few tumours of this kind have been cured by simple enucleation or irradiation. The following case exemplifies the disease.

Case 1—A healthy woman aged 46 had a slowly enlarging well-defined lump in the upper part of her neck for 8 years. It was thought to be a salivary tumour and was excised. It was an encapsulated slightly lobulated ovoid mass $5 \times 2.5 \times 2.5$ centimetres, consisting of uniform soft white tissue. *Histology*—Well-differentiated lymphoid tissue containing large follicles with germinal centres throughout.

(b) Multiple follicular lymphoma or lymphosarcoma

This has been well described by Symmers (1938 and 1942). It presents slow enlargement of one or more groups of glands with extension to other glands,

clinically less obtrusive abdominal disease, just as it is with some abdominal carcinomas. In my 34 necropsies the abdominal lymph glands were those most heavily involved and were considered to be the primary site of disease, in 22 cases.

The axillary or inguinal lymph glands, the tonsil pharynx, intestinal lymphoid tissue or spleen are all occasional primary sites of lymphosarcoma. It must be remembered, however, that tonsillar or pharyngeal carcinomas of anaplastic lympho-epithelial type (qv) have often been mistaken for lymphosarcomas, and that it is often difficult to be sure of the primary splenic or intestinal origin of an abdominal lymphosarcoma because in most cases by the time the tumour is seen many neighbouring lymph glands also are affected. Good accounts of primary intestinal lymphosarcomas include those of Jopson and White, Libman, Graves, Ullman and Abeshouse, Simpson Smith, and Webster.

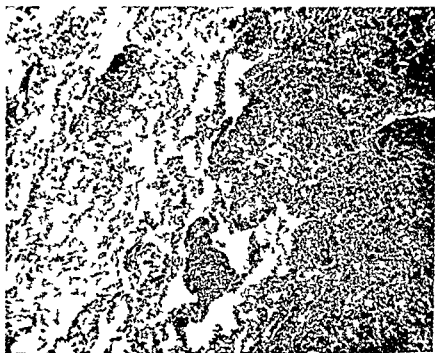


FIG 372—Case III Lymphosarcoma invading lung ($\times 80$)

The following case presented an extensive lymphosarcoma of lung tissue and only slight involvement of peribronchial lymph glands presumably therefore the tumour arose from the bronchial lymphoid tissue.

Case III—History—A man aged 57 had had 9 attacks of 'pneumonia' in the last 3 years. skiagrams showed large opacity in right upper lung field. Lobectomy was performed by Mr C J O Brown. The specimen showed a large mass of diffuse white agrowth 8 centimetres in main diameter extending from hilum of lobe to its outer surface where pleura was thickened and adherent. *Histology* (Figs 372-374)—Well differentiated lymphocytic sarcoma mainly diffuse but with trabeculae of hyaline collagenous tissue with a few poorly differentiated follicles. The tumour had completely obliterated lymph lung tissue in most places at its periphery it invaded this tissue via the inter alveolar septa and perivascular and peribronchial tissues. Carbonized hilar and peribronchial lymph glands contained only small deposits of tumour.

From a cytological survey of the literature it seems not unlikely that the distribution of primary sites of lymphosarcoma is nearly in proportion to the relative bulk

insensibly with the syncytial reticulosarcomas' as will be readily appreciated from almost any of the recent accounts of the latter

Lymphocytic leukaemia means the demonstrable presence of malignant lymphocytes or lymphoblasts in the circulating blood. It is not a species of disease but merely a concomitant of some lymphoblastic tumours, a concomitant the frequency of which is not only readily understood but was clearly to have been expected, from the natural mode of formation and mobilisation of lymphocytes. Leukaemia may appear during the progress of previously aleukaemic cases. In Gall and Mallory's series leukaemia was found in 48 per cent of cases of 'lymphocytoma' and 38 per cent of cases of lymphoblastoma.

Except for the demonstrable presence or absence of malignant cells in the circulating blood, there are no differences between lymphosarcoma and lymphatic leukaemia in either gross or microscopic pathology. Every possible combination and variation in the distribution of lesions is encountered—large localized lymphosarcomatous tumours with or without leukaemia, widespread involvement of many or all of the lymph nodes and other lymphoid tissues of the body constituting generalized lymphosarcomatosis, with or without leukaemia, and with any of these there may occur in other organs either well defined metastases or diffuse metastatic infiltrations. From microscopical examination of affected lymph nodes alone, it is impossible to distinguish leukaemic from non leukaemic cases.

(1) Age and sex incidence

(a) Age

Although not rare in youth, even in infancy lymphosarcoma is predominantly a disease of middle and old age. In Gall and Mallory's series the mean age at onset of 76 cases of lymphoblastoma was 40 years, and in 51 per cent of the cases the onset was at ages over 40, and of 118 cases of lymphocytoma the mean age at onset was 44 and 65 per cent began at ages over 40 years. The ages of my 34 necropsy cases of lymphosarcoma ranged from 14 to 78.18 (i.e. more than one half of them) were over 50 years old, and the mean age was 52 years.

(b) Sex

As in all other sub-groups of lymphoid tumours, males outnumber females, the ratio being 2 or 3 to 1 in most series. My 34 necropsies were on 25 males and 9 females.

(2) Site of origin

The site of origin of the tumours is not always clear. In many of those presenting as cases of leukaemia or of generalized lymphosarcomatosis the initial site of origin cannot be specified or can only be guessed at. In other cases a large tumour of a particular region suggests, but does not always prove, that the tumour began in this region.

The cervical, abdominal and mediastinal lymph nodes are the commonest initial sites, usually given in that order of frequency. The predominance of cervical growths, however, may be more apparent than real, because these are sooner noticed than those of the abdominal or thoracic glands, and because massive disease of the cervical glands may sometimes be secondary to earlier but

(b) Sex

There is a decided predominance of males over females in the ratio of 2.6 to 1 in Gall and Mallory's series. My biopsy and necropsy records concern 38 males and 11 females.

(c) Site

It is often stated that the cervical lymph glands are those most often first affected, but doubts like those already expressed regarding the primary sites of lymphosarcomas apply to many cases of Hodgkin's disease also. Cases of supposedly "primary splenic or intestinal Hodgkin's disease" also are seldom indubitable; these are usually only clinically primary in that splenomegaly or intestinal symptoms constituted the first signs of disease.

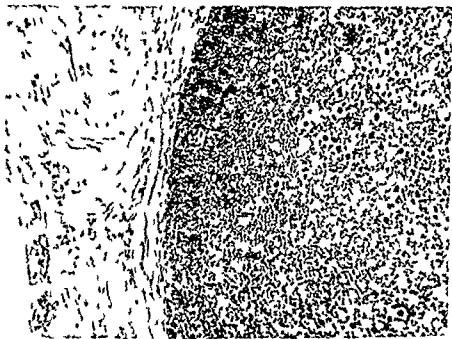


FIG. 377.—Cortical zone of a cervical lymph gland affected by early Hodgkin's disease in a man aged 19 showing loss of follicular pattern and many large multiplying reticular cells ($\times 120$).

(2) Structure and histogenesis

The characteristic but rather variable structure of Hodgkin's tissue is well described and depicted by Pullinger. In the early stages (Figs 377, 378), there is gradual loss of normal nodular architecture of the lymphoid tissue, the lymphocytes and their precursors tending to form instead diffuse sheets mingled with proliferating reticulum cells; this diffused lymphoid tissue contains few or many large conspicuous rounded or irregular cells measuring from $20\ \mu$ to $100\ \mu$ or more in diameter, containing single or multiple nuclei numbering up to 8 or more per cell, and showing many mitoses, eosinophil neutrophil and basophil granulocytes and plasma cells in variable numbers mingle diffusely or patchily with the proliferating tissue. In the later stages plentiful fibrous tissue develops first in bands separating lobules of the more cellular Hodgkin's tissue,

of lymphoid tissue in the different regions of the body, and that no particular part of the lymphatic system is disproportionately liable to neoplasia. The question

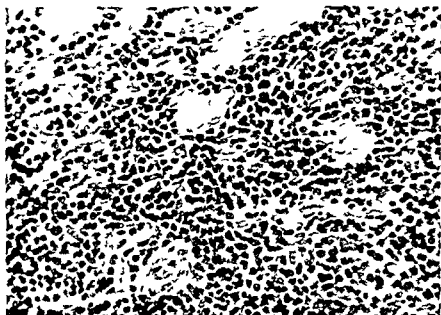


FIG. 373.—Case III. Hyaline trabeculae in lymphocytic growth ($\times 400$)

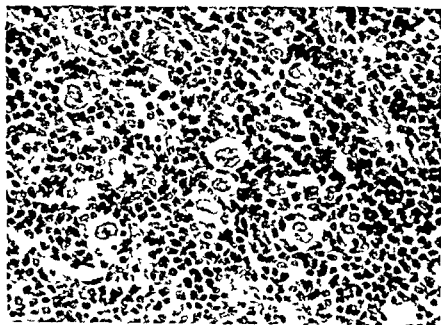


FIG. 374.—Case III. Large undifferentiated cells resembling those of Hodgkin's disease in lymphocytic growth ($\times 400$)

of multicentric origin is discussed below along with that of metastasis.

(3) Structure

It is unnecessary to repeat in detail the well-known features of

of Hodgkin's disease (Warthin, Gill and Mallory, Gill and McCall), and by the presence in acute Hodgkin's disease of areas of tissue indistinguishable from large celled lymphoblastomas. Lesions designated "Hodgkin's sarcoma" may contain areas of such tissue, or of tissue identical with that of syncytial reticulosarcoma, or of both.

The fibrosis of old Hodgkin's lesions may not be merely the result of stromal reaction, but may be a specific feature of the tumour tissue. Since the proliferating tumour cells are reticular, and since reticular proliferation in lymphoid tissue often participates in fibrosis, we might expect that a slowly growing Hodgkin's lesion should become densely fibrous, just as a slowly growing fibrosarcoma may do. Thus the chronic Hodgkin's lesion, in so far as it is a fibrosing lesion is a genuinely fibrifying tumour—a kind of fibrosarcoma of lymphoid tissue.

In my view then Hodgkin's disease is a tumour of primitive reticular cells in which divergent differentiation of both lymphoid and fibroreticular elements takes place. These elements are found in varying proportions and varying degrees of differentiation. When the growth is highly undifferentiated or anaplastic it becomes indistinguishable from, and indeed identical with, the undifferentiated stem cell or syncytial reticulosarcoma. Through Hodgkin's disease, all sarcomas of lymph glands are related.

The view that Hodgkin's tissue has myeloid affinities or potentialities seems to me to rest on insecure bases. These are three, namely, (a) the frequent admixture of granulocytes in the tissue (b) a supposed resemblance of Hodgkin's giant cells to megakaryocytes, and (c) the very occasional coexistence of Hodgkin's disease and myeloid leukaemia. As to (a), I doubt if any modern pathologist would seriously sustain the view that the granulocytes in Hodgkin's tissue are genetically related to and derived from that tissue. They are very variable in kind, number and distribution and have all the appearance of being immigrant reactionary leucocytes such as occur in many a carcinoma. As to (b), Medlar (1931), and Symmers (1938 and 1942) are as far as I know the only modern exponents of the view that the multinucleated cells of Hodgkin's disease are indeed bone marrow megakaryocytes, a view for which comparison of the two kinds of cells gives no support. As to (c), the coexistence of myeloid leukaemia and Hodgkin's disease has been reported so rarely (references by Forkner and by Gill and McCall), that the association may well be no more than fortuitous, and it must not be forgotten that myeloid reaction with or without eosinophilia, in cases of Hodgkin's disease with involvement of bones, might be mistaken for leukaemia. In view, then, of the very dubious relationship of any of the proper constituents of Hodgkin's tissue to those of bone marrow, it would be wise to avoid Pullinger's and Robb-Smith's name 'fibro myeloid reticulosis' for Hodgkin's disease. In any case, 'reticulosis' is a vague term, meaning only 'reticular proliferation' and contributing nothing to our understanding of the many and diverse lesions to which it has been applied.

The eponyms bestowed on the large multinucleated tumour cells of Hodgkin's disease call for comment. These are usually called 'Sternberg' or 'Reed' or 'Sternberg Reed' cells, because of Carl Sternberg's description in 1898 and Dorothy Reed's description in 1902. But in 1878 a symposium of the Pathological Society of London on diseases of the lymphatic system contained several contributions in which these cells were referred to. Thus Green

later more extensively replacing this tissue and sometimes converting almost the whole of an affected gland into a hyalinized fibrous mass. Small groups of large or multinucleated cells often persist here and there in densely fibrous areas and eosinophil leucocytes also are found in them.

Most workers agree that the essential proliferating elements in Hodgkin's tissue are the large and multinucleated cells—the so called "Sternberg Reed giant cells"—and that these are neoplastic reticulum cells. The granulocytes and plasma cells in Hodgkin's tissue appear clearly to be only reactionary elements similar to those seen in many other kinds of tumours. The two remaining components, namely, the lymphoid cells and the fibro reticular tissue, require special consideration.

In Hodgkin's lesions in lymphoid tissue itself, it is impossible to decide whether the plentiful lymphocytes and lymphoblasts which are present are essential tumour

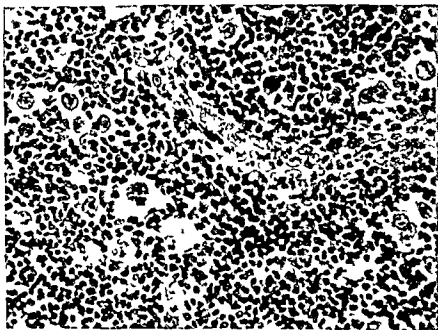


FIG. 378.—Detail of Fig. 377 ($\times 300$)

cells or are merely residues of the original tissue. But in secondary deposits of Hodgkin's tissue in the liver, lungs, skin or other non lymphoid structures, lymphoid cells are again present and are often plentiful, thus appearing to be an integral part of the lesions. We must conclude then, either that the neoplastic proliferation itself produces these cells, or that lymphocytes are attracted into and multiply in it wherever it occurs—as in lympho epitheliomas. Of these two alternatives there is strong, I think conclusive evidence in favour of the former. In Hodgkin's lesions it is impossible to distinguish with precision between immature lymphoid and immature reticular cells, and the varieties of size and shape of the cells encountered strongly suggest that all of these are tumour cells differentiating from a stem-cell precursor in two divergent directions. This concept is supported by the not infrequent occurrence of lymphocytic leukaemia in cases

by a large hard mass of growth adherent to sternum ribs and clavicles invading and partly replacing upper lobe of right lung and surrounding and invading superior vena cava. Right main bronchus was surrounded by growth in bronchial lymph glands and its mucosa showed a nodular ulcerated plaque 2.5 centimetres in diameter. Both lungs contained also multiple discrete areas of white growth the largest 5 centimetres in diameter and nodules and plaques of growth were present in right pleural cavity. Thyroid was invaded from cervical glands and largely replaced by growth. Liver contained only one small white nodule. Spleen and alimentary canal normal and no deposits found on section of skull sternum and vertebrae. Necropsy diagnosis carcinoma of right bronchus with extensive lymphatic metastases. *Histology*—Typical chronic Hodgkin's disease with multinucleated cells much dense fibrosis and many eosinophil leucocytes. (*Comment*—The case is notable not only because of the bronchial lesion but also because of the presence of a large mediastinal tumour and gross invasion of a main vein.)

Case VII—Female aged 39. *Symptoms*—Clinical and radiographic signs of large anterior mediastinal tumour. *Necropsy*—Hard white irregular nodular tumour 10 centimetres in main diameter lay in upper anterior mediastinum enveloped the aortic arch and adhered to base of heart and to vertebrae and first rib. Sections showed peripheral parts of the growth to include enlarged coalescing lymph glands. Its central parts contained many areas of suppuration ramifying from an area of necrotic ulceration 2 centimetres in diameter in lumen of left bronchus. Left lung was collapsed and showed patchy pneumonia. Right hilar lymph glands contained small deposits of firm white growth. All other groups of glands and other viscera including spleen appeared normal. Necropsy diagnosis infected mediastinal tumour. *Histology*—Bulk of growth consists of dense hyaline fibrous tissue with patches of lymphocytes plasma cells and eosinophil granulocytes but parts near root of lung and in bronchial wall show typical active Hodgkin's disease.

Case VIII—Male aged 75. *Symptoms*—Debility and dysphagia for 4 months and enlarged cervical and axillary glands both sides. clinical diagnosis ? gastric carcinoma. *Necropsy*—Moderate enlargement of cervical axillary all mediastinal and retroperitoneal lymph glands those of right axilla coalescing to form an irregular infiltrating mass 8 centimetres in diameter adherent to ribs and muscles and showing much yellow degeneration. Hilum of left lung contained an irregular friable mass surrounding main bronchus and ulcerating into it at several places but not invading lung tissue. Spleen not enlarged but studded with firm white nodules. Other organs all appeared normal. Necropsy diagnosis ? Hodgkin's disease ? bronchial carcinoma. *Histology*—Cellular Hodgkin's disease—Hodgkin's sarcoma—with many large and multinucleated cells with many mitoses. Axillary mass shows unusually extensive necrosis.

(b) Hodgkin's deposits in bones

These are present in the majority of fatal cases, and would perhaps be found in nearly all if searched for (Uehlinger, Steiner). While bones may be invaded directly from neighbouring lymph nodes (as in Uehlinger's Figs 6, 8 and 9) most of the skeletal lesions are clearly blood borne metastatic deposits in red bone marrow. They have a distribution similar to that of other kinds of metastatic growths the bones most frequently affected being the vertebrae pelvis sternum ribs, and proximal end of the femur. They appear usually as multiple discrete or confluent areas of white tissue not to be distinguished by the naked eye from other metastatic tumours. They are often unsuspected clinically but may lead to radiographically obvious lesions, to tumefaction of the bone or to pathological fracture. Weigall and Derrick reported a remarkable case in which vertebral lesions gave the first signs of disease and simulated tuberculous caries and in which a circumscribed deposit caused prominent expansion of the head of a

glands of Hodgkin's disease— In the early stages there was some general enlargement of the glands the fibrous stroma appeared coarser, and there were a large number of multinucleated cells adherent to the trabeculae, well seen on washing away the lymph cells. These multinucleated cells containing from four to eight or twelve nuclei, were often collected in clusters in the parts of the gland especially where the fibrous change was progressing. Greenfield clearly depicted these cells and in the spleen also he saw 'cells of various sizes massed together, a good many large multinucleated cells being amongst them'. At the same time, Sutton also saw in Hodgkin's lymph glands many large and very conspicuous cells of round or oval form, and having a considerable amount of protoplasm around the nuclei, and in the spleen "large cells, many of them polynucleated, similar to those seen in the lymphatic glands. Coupland too, referred to numerous large nucleated cells occurring mingled with the smaller lymphoid cells'. In the same year as Dorothy Reed's paper Andrewes also independently described the large cells of Hodgkin's disease. Hence if Dorothy Reed's name is to be retained eponymically, we shall have to employ a compound title including the names of at least 6 writers!

(3) Spread, metastasis, and the question of multifocal origin

The discussion already given regarding the parts played by metastasis and systemic origin in the extension of lymphosarcomas applies *mutatis mutandis* to Hodgkin's disease. While study of early Hodgkin's changes in lymph nodes makes it clear that in some cases the disease arises multifocally or diffusely within a particular territory of lymphoid tissue it is equally clear that metastatic spread from node to node or by the blood stream plays an important part in its dissemination. Small lymphatics and veins are often to be found invaded by Hodgkin's tissue and arteries and large veins also are invaded (see Uehlinger's Figs 18 and 19 and Case VI below). Even if one were prepared to suppose that all lesions in lymphoid and other haemopoietic tissue were multiple autochthonous foci and never metastases, this could scarcely apply to circumscribed lesions in the lungs skin nervous system and other non haemopoietic organs. In the liver, spleen and bone marrow also while in some cases Hodgkin's infiltrations are diffuse or only indefinitely nodular in other cases the deposits form well defined white masses set in organs showing little or no evidence of diffuse involvement just like any other metastatic growths.

(a) Involvement of the lungs and mediastinum

This deserves special comment. It may occur as scattered metastatic deposits in the lung substance or as extensions from disease of the hilar or mediastinal lymph glands or as a large mediastinal tumour. Hilar lesions may surround and invade the main bronchi and so may be indistinguishable grossly from bronchial carcinoma as in the following cases.

Case 11—History—A man aged 21 developed a mass in lower left part of neck further masses appeared later in other parts of neck and both axillae. These were diagnosed clinically as Hodgkin's disease and treated by X rays and arsenicals with benefit. Recurrences however appeared including a large mediastinal mass seen in skiagrams and the man died at the age of 25. *Necropsy*—Hard enlargement of lymph glands in all parts of body partly discrete partly diffuse and confluent. Anterior mediastinum occupied

The only tumours to which the term 'reticulosarcoma' is strictly applicable are those in which differentiation of reticular tissue type is distinct and predominant. These tumours used to be called 'endotheliomas' of lymph glands, a diagnosis however, which was often erroneously made also in cases of metastatic carcinoma. It cannot be too strongly insisted that complete and careful necropsy study is often the only means of establishing—or refuting—the primary nature of an anaplastic tumour of uncertain nature in a lymph gland. Of Roulet's much quoted paper (1930) it is to be noted that in many of his cases of "Retothelsarkom" no necropsies were performed, and that some of his figures (e.g. Figs 7 and 8) might well be diffuse carcinoma. Until this source of confusion is eliminated, it will not be possible to make a reliable analysis of the properties of the true reticulo sarcomas of lymphoid tissue. Most of these tumours have occurred in adult males, have consisted of spindle celled or pleomorphic celled tissue, and have shown a tendency to spread from gland to gland as well as by the blood stream.



FIG 379—Case X Reticulosarcoma of epitrochlear lymph gland ($\times 120$)

I have performed necropsies on three cases in which the final diagnosis was reticulum cell sarcoma of lymph glands, in two cases there were also features resembling Hodgkin's disease. These cases were briefly as follows:

Case Y—(Reported in 1934 p. 437 No. 57) Male aged 66. Spindle-celled sarcoma of epitrochlear lymph gland with extension to axillary and supraclavicular glands and metastases in lung, myocardium, adrenals, pancreas, mucosa of ileum and colon, peritoneum, skull and skin (Fig. 379).

Case X—Male aged 43. *Symptoms*—Enlarging mass recently noticed in left side of neck was excised and found to consist of an enlarged lymph gland replaced by soft white tissue. Microscopically this consisted of undifferentiated cellular polyhedral celled growth with many mitoses of uncertain nature, possibly primary sarcoma, possibly secondary anaplastic carcinoma. Deep X-ray therapy was applied to neck and there

rib Uehlinger described several examples of vertebral collapse and paraplegia from Hodgkin's disease, and also an unusual sternal deposit with vertical spicules of periosteal new bone radiographically misdiagnosed as 'osteogenic sarcoma'. The following case was unusual both because bone lesions caused the first symptoms of the disease and because of the patient's age

Case IX—(From Dr Basil Jones of Horsham Victoria) History—Female child aged 4 years had had pain and limitation of movement of right shoulder for 6 months. On examination the only other abnormalities were moderate enlargement of right axillary lymph glands and doubtfully palpable spleen. Skiagrams showed an area of decalcification of the humerus 4 centimetres long involving the inner aspect of the shaft just below the head and extending into the head and epiphysis. *Histology*—Enlarged gland removed from axilla showed typical Hodgkin's disease with fibrosis many multinucleated cells and many eosinophil leucocytes

(4) Gordon's test

Gordon's discovery (1932) that intracerebral inoculation of rabbits with Hodgkin's tissue usually produces a characteristic encephalitis but that tissue from other lesions of lymph nodes or from normal nodes rarely does so has been repeatedly confirmed. Positive results have been obtained in three quarters of the cases of Hodgkin's disease tested (Steiner). That the test is not specific, however, is shown by the positive results obtained with normal bone marrow, spleen and occasionally some other tissues. That it is probably due not to a virus but to some chemical substance or enzyme is shown not only by these positive results with normal tissues but also by the fact that attempts to transfer the encephalitis from rabbit to rabbit have failed. Edward Robb Smith and Turner *et al* have advanced strong evidence that the agent responsible for Gordon's test resides in the granular leucocytes, especially the eosinophils, and that it is by virtue of the presence of these cells in considerable numbers in Hodgkin's lymph nodes that these give a positive result. Robb Smith obtained positive results from eosinophil infiltrated lymph nodes in trypanosomiasis and idiopathic eosinophilia.

RETICULUM CELL SARCOMA

We have already concluded that Hodgkin's disease in so far as it is a malignant tumour of the reticulum cells of lymphoid tissue is a form of reticulum cell sarcoma. This term is, however, more strictly applied to tumours in which the predominant or only line of differentiation of the neoplastic cells is towards reticular connective tissue i.e. to fibrifying tumours allied to fibrosarcomas. It has also been extended to include the undifferentiated or anaplastic 'syncytial reticulosarcomas' which however are not sharply separable from other anaplastic sarcomas of lymphoid tissue—Hodgkin's sarcomas and primitive lymphoblastomas. As regards all of these anaplastic growths indeed it is necessary to recall—what should be obvious—that their very anaplasia renders attempts to sub-divide them inadvisable. Structurally they can be identified no more specifically than as anaplastic sarcomas. In my opinion Hodgkin's sarcoma 'diffuse syncytial reticulosarcoma', 'trabecular syncytial reticulosarcoma', 'dictosyncytial reticulosarcoma', and 'lymphoblastic reticulosarcoma' are not separable but are only arbitrary names for variants of the same thing.

While there is little doubt that the growths in these three cases were primary tumours of lymph glands I confess to some indecision as to their most appropriate names in spite of careful histological study. They were provisionally called reticulosarcomas, but the tumour of Case X might equally well be called simply "spindle celled sarcoma" while those of Cases XI and XII might equally well be called "atypical Hodgkin's disease". From the cases recorded by others as reticulosarcomas I suspect that similar indecision might well have obtained in some of these though not admitted by the authors.

Kaposi's sarcoma

This peculiar disease may be conveniently mentioned here. It has been studied mainly by dermatologists and has been variously regarded as a granuloma round celled sarcoma, angiosarcoma, haemangioma, endothelioma, reticulosarcoma and a peculiar form of fibrosarcoma (Symmers 1941). While the long duration of the disease, often many years, the great predominance of males, the high proportion of Jewish patients, and the appearance and course of the skin lesions, certainly suggest a pathological entity, the histopathology of recorded cases has been very variable and non distinctive. The only case which I have personally studied, in which the lesions resembled those commonly described as Kaposi's disease, was Case XII above, and I feel confident that this was one of fibrifying reticulo sarcoma of lymph glands with plentiful admixed lymphocytes. This experience leads me to wonder if Kaposi's disease may not be one of the many variants of lymphoid tumours with prominent skin lesions related to those of Hodgkin's disease and mycosis fungoides. Such a histogenesis would not exclude Symmers's view that it is a peculiar form of fibrosarcoma, for fibrosing Hodgkin's disease and reticulosarcomas also are peculiar forms of fibrosarcoma. Additional careful necropsy studies of cases of this disease are needed.

TUMOURS OF LYMPHOID TISSUE IN ANIMALS

Leukaemic and non leukaemic lymphoblastomas are amongst the commonest tumours of many species of animals. According to Feldman they account for about one third of malignant growths in cattle and pigs and 15 per cent of those in sheep; they are common also in dogs, mice, rats and birds, and rather less common in cats, horses and rabbits. (See also Englebreth Holm.) Stasney and Feldman made a particularly thorough study of a case of lymphocytic leukaemia in a calf. Of the many papers on lymphoid tumours and leukaemias in mice, those of Furth *et al* (1933 and 1935), McDowell, McDowell and Richter, and Potter *et al* are valuable sources of reference. Lymphoid tumours in animals have been variously designated by the same names as the human ones—lympho sarcoma, lymphatic leukaemia, Hodgkin's disease, etc.—and it is clear from the animal tumours, as from the human, that these are but variants of a single group of tumours. As both Rolleston and Feldman have pointed out, the propriety of the term "Hodgkin's disease" in reference to most animal tumours is questionable, the histology of the lesions has seldom been so characteristic as to prove its identity with the human lesion. However, Stalker *et al* have described an acceptable example of Hodgkin's disease in a dog. Most lymphoid growths in animals are lymphosarcomas with or without leukaemia.

was no recurrence of tumour. Patient died 4 months later from acute right lobar pneumonia. *Necropsy*—Several lower cervical lymph glands were slightly enlarged but did not appear diseased. thoracic and abdominal glands all appeared normal. Except for pneumonia all viscera including all cranio-cervical structures were normal. *Histology*—Some cervical lymph glands are replaced by fibrous and cellular tissue containing many large polyhedral cells some of which are in mitosis. there are also many plasma cells but no eosinophils. Some of the non-enlarged mediastinal glands show small patches of similar tissue with a few eosinophils more closely resembling Hodgkin's disease.

Case XII—Female aged 26. *Symptoms*—Emaciation recurrent pyrexia and persistent skin eruption diagnosed as pemphigus. *Necropsy*—Lungs contained scattered areas of firm grey or haemorrhagic tissue. hilar glands were enlarged by similar growth. Liver contained many small scattered ill-defined areas of soft white tissue. portal glands were greatly enlarged by firm white growth. Spleen contained many small white nodules. Retroperitoneal and mesenteric lymph glands enlarged and haemorrhagic. cervical glands not enlarged but similarly affected. inguinal and axillary glands normal. Mucosa of stomach and small intestine contained multiple firm white or haemorrhagic nodules up to 1 centimetre in diameter many with central ulceration. Skin showed extensive but patchy infiltration by white or haemorrhagic tissue. Skull contained several small ill-defined areas of soft tissue involving dura. Other bones and viscera normal. *Necropsy diagnosis* abdominal Hodgkin's disease. *Histology* (Fig 380)—Affected lymph glands and deposits in liver lungs intestine spleen and skin show mingled fibro-sarcomatous and polyhedral-celled growth with many mitoses accompanied by many lymphocytes and monocytes but no eosinophil leucocytes. The tissue contains plentiful small blood vessels. areas of haemorrhagic necrosis are common. *Diagnosis*—Though not typical of any the tumour shows similarities to Hodgkin's disease to fibrosing reticulosarcoma and to Kaposi's haemorrhagic sarcoma. It was classified as a primary reticulosarcoma of the upper abdominal lymph glands with metastases to other parts.

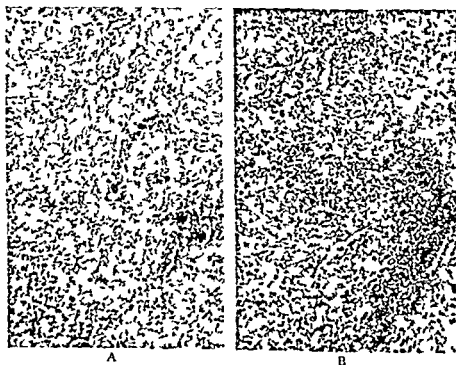


FIG 380—Case XII Diffuse fibrosing reticulosarcoma with admixed lymphocytes. A = from lymph gland B = from liver ($\times 100$)

lymphoid tissue as related variants of one disease. The names used for the principal variants have descriptive and clinical value but do not denote distinct pathological entities. *Follicular lymphoma* is the least malignant, best differentiated variant of the group, with a structure approaching that of normal lymphoid tissue. *Lymphosarcomas* show predominant differentiation of neoplastic lymphocytes or lymphoblasts. *Lymphatic leukaemia* is lymphosarcoma with a circulating metastasis. *Hodgkin's disease* shows differentiation of both lymphoid cells and reticular elements, the latter often fibrifying. *Reticulosarcoma* is a name best reserved for tumours showing predominant reticular (i.e. fibrifying) tendencies, it is better not to apply it to anaplastic syncytial growths devoid of differentiation.

Mycosis fungoides is only a form of skin lesion of one of the foregoing variants, perhaps the same applies to some cases of *Kaposi's disease*.

REFERENCES

- Andrewes F W (1902) *Trans Path Soc Lond* 52 305
 Berman L (1940) *Arch Path* 29 530
 Callender G R (1934) *Amer J Path* 10 443
 Coupland S (1878) *Trans Path Soc Lond* 29 363
 Dawson E K, Innes J R M and Harvey W F (1937) *Edinb Med J* 41 645
 Edward D G (1938) *Lancet* i 936
 EHRlich, J C, and GERBER, J E (1935) The histogenesis of lymphosarcomatosis
Amer J Cancer 24 1 (A careful study of 18 necropsy cases)
 Engelbreth Holm J (1946) *Proc Roy Soc Med* 39 735
 Feldman W H (1932) *Neoplasms of Domesticated Animals* Chapter VIII Philadelphia
 Forkner C E (1937) *Arch Int Med* 60 582
 FORKNER, C E (1938) *Leukemia and Allied Disorders* New York (A comprehensive monograph with full bibliography)
 FURTH J, SIEBOLD, H R and RATHBONE, R R (1933) Experimental studies on lymphomatosis of mice *Amer J Cancer* 19 521 (An excellent well illustrated account of transmissible leukaemic and non leukaemic tumours)
 FURTH, J, FERRIS H W, and REZNIKOFF, P (1935) Relation of leukemia of animals to leukemia of man *J Amer Med Assoc* 105 1824 (An excellent outline of the comparative pathology)
 Furth J and Kahn M C (1937) *Amer J Cancer* 31 276
 GALL E A and MALLORY, T B (1942) Malignant lymphoma. A clinico-pathologic survey of 618 cases *Amer J Path* 18 381
 Gill A W and McCall A J (1943) *Brit Med J* i 284
 GINSBURG, S (1934) Lymphosarcoma and Hodgkin's disease. biologic characteristics *Ann Int Med* 8 14 (A good historical review of the opposing views regarding the relationship of the two diseases)
 GORDON, M H (1932) *Studies of the aetiology of lymphadenoma* p 7 Rose Research
 Greenfield W S (1878) *Trans Path Soc Lond* 29 272
 HERBUT P A, MILLER F R and ERIK A L (1945) The relation of Hodgkin's disease lymphosarcoma and reticulum cell sarcoma *Amer J Path* 21 233 (A good account upholding the unitarian view)
 Jopson J H and White C Y (1901) *Amer J Med Sci* 122 807
 Libman E (1900) *Amer J Med Sci* 120 309
 Mallory F B (1914) *Principles of Pathologic Histology* Philadelphia
 MacCormac H (1941) *Brit Med J* ii 645
 MacDowell E C (1936) *Amer J Cancer* 26 85
 MacDowell E C and Richter M N (1935) *Arch Path* 20 709
 Medlar E M (1931) *Amer J Path* 7 499
 Naegeli O (1932) (Translated by Weber F P) *Brit med J* ii 922
 Nieberle K and Cohrs P (1931) *Lehrbuch der Speziellen Pathologischen Anatomie der Haustiere* Jena

As Furth and his co workers have insisted, the pathology of animal tumours closely parallels that of the human ones in almost every respect, and there is no doubt that the disease is essentially the same in all species of mammals. It is however, doubtful whether fowl leukaemia and other avian 'leucoses' are analogous to the mammalian diseases. The bird lesions differ in some respects from the mammalian ones and the presence in them of a filterable causative agent also makes them peculiar—just as the filterable avian sarcomas typified by Rous's tumour are peculiar and doubtfully comparable with mammalian sarcomas. As Furth and his co workers have shown the transfer of mouse leukaemia from one animal to another is possible only by the transfer of living intact leukaemia cells and not by injured cells or cell free extracts. Furth and Kahn found that a single intact leukaemic cell sufficed for the transfer of leukaemia from one mouse to another.

Rudduck and I in our necropsies on dogs frequently observed in the spleen a lesion which we could not find adequately described in the literature and which has all the appearances of a lymphoid tumour. This consists of single or multiple, fairly well defined but not sharply circumscribed nodular growths usually 1 to 3 centimetres in diameter but sometimes larger composed of white tissue mottled by haemorrhage and microscopically consisting of lymphoid tissue aggregated indefinitely in nodules and intervening strands of congested haemorrhagic or pigmented reticular tissue showing some fibrosis and often containing multi nucleated cells. These lesions are usually found only incidentally in animals dying from various causes and without evidence of lymphoid tumours elsewhere. The possibility of the growths being infective lesions was not overlooked but careful search of Giemsa stained and Gram stained sections regularly failed to reveal any bacteria and guinea pig inoculations gave negative results. It seems possible, then that these lesions constitute a special variety of relatively benign localized lymphosarcoma or lymphoma of the dog's spleen.

CAUSATION OF TUMOURS OF LYMPHOID TISSUE

So far there is very little substantial evidence either human or experimental pointing to the causative agents of lymphoid tumours. Leukaemias developing in persons exposed to benzol or to X rays are usually of the myeloid variety (see Chapter 51). Lymphocytic leukaemias in such persons (e.g. those reported by Falconer and by Tarcey cited by Hueper) are so rare that the occupational association is probably only fortuitous. Leukaemoid reactions are observed in animals treated with carcinogenic hydrocarbons, and these substances also cause an increased incidence of lymphoid tumours or leukaemia in strains of mice prone to these diseases (see Chapter 4) but there is no evidence that occupational exposure to carcinogenic hydrocarbons increases the risks of leukaemia or lymphosarcoma in man. However, more thorough inquiry into the past habits and occupations of the victims of these complaints is needed and may eventually discover some of the responsible agents. The marked predominance of males certainly suggests that occupational factors may well be concerned.

CONCLUSION

I join Warthin, Ginsburg, Herbut *et al.* and others who regard all tumours of

CHAPTER 50

PLASMOCYTOMAS AND MYELOMATOSIS

TUMOURS consisting of plasma cells are of the following three kinds

- Plasma cell myelomatosis
- Solitary plasmocytoma of bone
- Primary plasmocytoma of soft tissues

Although in a minority of cases of multiple myelomatosis the tumour cells are not distinctly plasma cells and have received other designations in most cases the tumours plainly consist of plasma cells and the disease as a whole is best considered in this context. To the debate regarding the histogenesis of plasma cells, the study of plasma cell tumours has a contribution of value to make

MULTIPLE MYELOMATOSIS

(1) Personally studied cases

The following cases exemplify the main clinical and pathological features of the disease

Case I—Female aged 48. *History*—Recent pain in back, of sudden onset. skiagrams showed multiple decalcified areas in vertebrae. 'myelomatosis' ? metastatic growths ? no Bence Jones protein found in urine. *Necropsy* showed many soft greyish tumours in bone marrow of skull vertebrae ribs and pelvis with partial collapse of several vertebrae and pathological fractures—some healed—of ribs. No tumours in viscera. *Histology*—Typical cellular plasma-cell growths with some multinucleated cells. Viscera clear

Case II—Male aged 42. *History*—After extraction of teeth bleeding persisted and proved fatal 18 days later. *Necropsy* showed many rounded pale soft growths up to 1 centimetre in diameter, in vertebrae sternum ribs and pelvis but none obvious in femur or skull. No tumours in viscera. *Histology*—Growths consist of typical well differentiated plasma cells some multinucleated (Fig 381)

Case III—Male aged 58. *History*—Pain in back and loss of weight for some months test meal showed achlorhydria. clinical diagnosis carcinomatosis probably from primary in stomach. Albuminuria by ward tests. *Necropsy*—Many small rounded soft greyish tumours present in all vertebrae ribs sternum clavicles pelvis and femora with partial collapse of several vertebrae. No tumours in skull or in viscera. *Histology*—Typical plasma-cell tumours with some multinucleated cells. Viscera clear. Kidneys show patchy calcification within the tubules

Case IV—Male aged 81. *History*—Severe pains in shoulders and left arm for some months. Extensive destructive lesion of the seventh cervical vertebra seen in skiagrams. ? myeloma ? metastatic growth. *Necropsy*—Lower two cervical vertebrae largely replaced by soft brownish tissue a few discrete soft tumours present in other vertebrae fusiform enlargement of several ribs by growth. no tumours found in sternum pelvis femora or skull. Right lobe of thyroid enlarged by an irregular cystic mass which was thought to be possible primary carcinoma with metastases in bones. *Histology*—Typical plasma-cell myelomatosis

Case V—Female aged 64. *History*—Pains in chest and loin for 2 months, more recent left facial oculomotor paralysis and paresis of limbs. Ward tests albuminuria constantly present. Clinical diagnosis Landry's paralysis. *Necropsy*—Skull

- Potter J S Victor J and Ward E N (1943) *Amer J Path*, 19 239
- PULLINGER B D (1932) *Histology and Histogenesis* p 115 Rose Research on Lymph adenoma (An excellent well illustrated account)
- Robb Smith A H T (1938) *J Path Bact* 47 457
- Rolleston H (1926) *Brit Med J* 1 230
- Roulet F (1930) *Virchows Arch* 277, 15
- Simpson Smith A (1938) *Brit J Surg* 26 429
- Stalker L K Schlotthauer C F and Feldman W H (1936) *Amer J Cancer* 28 595
- Stasnev J and Feldman W H (1938) *Amer J Cancer* 34 240
- Stasney J and Downey H (1935) *Amer J Path* 11 113
- Steiner P E (1941 and 1943) *Arch Path* 1941 31 1 1943 36 627
- Stout A P (1942) *J Amer Med Asso* 118 968
- Sutton (1878) *Trans Path Soc Lond* 29 342
- Symmers D (1938 1941 and 1942) *Arch Path* 1938 26 603 1941 32 764 1942 34 385
- Turner J C Jackson H and Parker F (1938) *Amer J Med Sci* 195 27
- UEHLINGER E (1933) Über Knochen Lymphogranulomatose *Virchows Arch* 288 36
(An excellent study of Hodgkin's lesions in bones)
- Ullman A and Abeshouse B S (1932) *Ann Surg* 95 878
- Warren S and Picena J P (1941) *Amer J Path* 17 385
- WARTHIN, A S (1931) The genetic neoplastic relationships of Hodgkin's disease aleukaemic and leukaemic lymphoblastoma and mycosis fungoides *Ann Surg* 93 153 (A succinct authoritative statement of the unitarian view)
- Wergall G R and Derrick E H (1928) *Med J Austral* 11 532
- Willis R A (1934) *The Spread of Tumours in the Human Body* London

or mushroom shaped masses projecting from bone surfaces. Pelvis ribs and femora contained scattered growths several of the ribs with projecting nodular or fusiform masses and pathological fractures. Viscera contained no tumours. *Histology*.—Tumours consisted of masses of rounded cells of undetermined kind with eccentric spherical or ovoid nuclei resembling myeloblasts or lymphoblasts more than plasma cells. Some multinucleated cells were present and some areas showed much fibrous tissue mingled with the round celled growth.

Case VII.—(Reported 1930) Female aged 59 with clinically diagnosed myelomatosis and Bence Jones proteosuria. Multiple but not numerous large tumours in several parts of skeleton including skull a rib manubrium sterni acromion a metacarpal clavicle humerus ischium femur tibia calcaneus talus and two metatarsals. Pathological fractures with sound union and good response of individual tumours to radium or X rays were notable features. *Histology*.—(biopsy from rib) cellular growth composed of round cells of undetermined kind unlike plasma cells and more like myeloblasts or lymphoblasts multinucleated cells present.

(2) Incidence

(a) Frequency

Myelomatosis is not a rare disease in various series it constitutes from 3 to 25 per cent of all primary malignant tumours of bones. Because of diagnostic errors, it is impossible to estimate its frequency accurately, not a few early cases escape clinical detection and are disclosed only at necropsy (e.g. Cases II III V and VI above) while in other cases the bone lesions are discovered radiographically but distinction from metastatic growths is difficult or impossible (e.g., Cases I and IV above). Conversely, metastatic growths in bones may be mistaken radiographically for the lesions of myelomatosis (Cosin).

(b) Age and sex

Three-quarters of the cases occur between the ages of 40 and 70 the mean age is in the sixth decade and the disease is very rare under 30 (Geschickter and Copeland Batts). Men are affected about twice as frequently as women.

(3) Distribution and appearance of the tumours in the skeleton

By radiographic examination, Batts found evidence of tumours in the various bones in the following percentages of cases—skull 73 spine 70 ribs 68 pelvis 63 femur 48 humerus 43, shoulder girdle 40 per cent and the bones of the peripheral parts of the limbs only occasionally. The vertebrae and ribs contained growths in all 6 of my necropsy cases and the pelvis in all but one case, but in 3 cases the skull contained no tumours obvious to the naked eye. The sternum frequently contains tumours. My Case VII was unusual in showing multiple large growths in the bones of the feet. Estimates of the frequency of involvement of various bones based on radiographic or routine necropsy examinations are of course underestimates not only because such examinations are rarely complete but also because diffuse myelomatous change as in Cappell's and Churg and Gordon's cases might easily escape naked eye or radiographic detection.

The tumours appear as soft sometimes almost fluid grey, pink or red growths replacing the bone marrow and accompanied by absorption of the bone trabeculae. They are usually well defined and nearly spherical and produce well demarcated

vertebrae ribs sternum and pelvis contained many large soft growths one of these extensively invaded dura over left optic foramen and cavernous sinus region several vertebrae showed partial collapse and large paravertebral masses of growth Multiple small white tumour nodules present in lungs liver spleen kidneys pancreas thyroid and mucous membranes of stomach and small intestine the largest being in the gastric

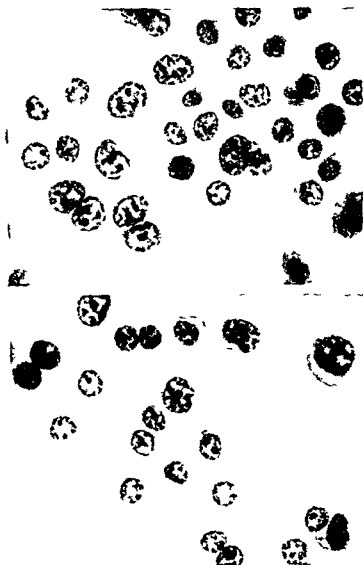


FIG 381—Case II Smear of myeloma plasma cells including some with two nuclei ($\times 1000$)

mucosa and measuring 2 centimetres in diameter *Histology*—In all situations tumours consisted of typical plasma cells with many mitoses and some multinucleated cells Liver in addition to visible tumour nodules showed diffuse plasma-cell infiltration of portal tracts and splenic pulp contained many plasma cells

Case 11—Female aged 65 *History*—Loss of weight and indigestion for 9 months clinical diagnosis carcinoma of colon *Necropsy*—Skull contained many rounded soft pinkish grey tumours which adhered to both dura and pericranium All vertebrae contained similar growths several of which perforated cortex and formed hemispherical

(5) Metabolic aspects of myelomatosis**(a) Bence Jones proteinuria**

This is demonstrable in more than one-half of the cases, but is often intermittent and so escapes detection (Wallgren, Geschickter and Copeland, Batts). Moreover, unless this substance is suspected and deliberately searched for, it is apt to be passed over as "albumen" in routine ward tests as probably happened in my Cases III and V. Bell has given a good general account of Bence Jones protein and Apitz has discussed in detail the disturbances of protein metabolism in myelomatosis. Abnormal proteins are produced in the tumour cells, appearing as rounded iuchsinophil masses (Russell's bodies) or as crystals. Abnormal protein deposits may develop in various mesenchymal tissues and lead to the 'amyloid disease' which occasionally accompanies myelomatosis. The intestine is an important site of massive amyloid deposits (Randall). Amorphous or crystalline deposits sometimes develop in the renal tubules (Lohlein, Bell, Gunn and Mahle). Further investigation is needed in order to determine whether these various deposits actually consist of Bence-Jones protein or some other allied substance or of some other abnormal metabolite.

(b) Renal failure

The renal insufficiency which often complicates the later stages of myelomatosis is sometimes due to purely incidental causes, such as arterial disease or pyelo-nephritis, but in some cases it appears to be due to obstructive precipitates in the renal tubules (Lohlein, Bell, Newns and Edwards, and possibly in my Case III).

(6) Tumours in soft tissues and the question of metastasis

In many cases of myelomatosis the tumours are restricted to the skeleton but in a proportion of fatal cases—perhaps one third or one quarter of them—localized tumours or diffuse infiltrations of the characteristic cells are present in viscera or other soft tissues. The organs most frequently affected are liver, spleen, lymph glands and kidneys, but deposits have been seen also in the lungs, heart, skin and subcutis, adrenals, thyroid, testes, ovaries, intestines, stomach, pancreas, uterus, and dura mater (Lohlein, Batts, Churg and Gordon, Newns and Edwards, Armstrong *et al*, and my Case V).

Are the multiple tumours in bone marrow and the deposits in soft tissues produced by metastasis or by multifocal origin? Probably both processes participate. There is no doubt that the tumours in bones arise multifocally as a system disease of the bone marrow, these growths are often similar in size with no one tumour more than another specifiable as primary, and they are often very numerous or diffuse while the lungs and other viscera show no secondary deposits. While multifocal origin may also be admitted as possible in lymphoid tissues, spleen and liver, metastatic colonization more plausibly accounts for myeloma deposits in these organs and especially for deposits in the kidneys, lungs, and other organs devoid of haemopoietic functions. It is probable then that both widespread origin in susceptible tissues and metastatic dissemination of tumour cells occur in myelomatosis just as they clearly do in the leukaemias (q.v.). Indeed 'plasma cell leukaemias' have been recorded (references by Churg and Gordon), and

rounded radio translucent areas in skiagrams. Radiographic distinction from multiple metastatic growths is often impossible. Small tumours produce no clinical tumefaction of the bones and are to be detected only by skiagrams or necropsy section of the bones. Larger tumours distend or destroy the cortex project from the bone surfaces, and produce egg shell crackling or pathological fractures. The fractures may reunite firmly. Spontaneous fluctuation in size or retrogression of individual tumours is not unusual.

(4) Microscopic structure and histogenesis

In 1921 Wallgren in a collected series of 125 cases of myelomatosis found 35 of plasma celled structure. Later studies, however, place the percentage much higher than this. e.g. Batts found that in 18 of his 23 microscopically examined cases the tumours were plasmocytomas and this applied also to 5 of my 7 cases. Identification of the plasma cells is often readily made in smears or sections stained by ordinary methods, but is aided by Unna Pappenheim or other special stains.

In cases in which the tumour cells have not been identified as plasma cells, they have usually been regarded as myeloblastic and sometimes as lymphoblastic or erythroblastic. However, the nature of the cells in these cases is, I think, often very doubtful and there is no justification for attempting to subdivide the disease on the grounds of this or that writer's arbitrary identification of the cells. Certainly in my own Cases VI and VII the identity of the tumour cells remains uncertain: they may have been myeloblasts, or lymphoblasts or immature plasma cells—indeed any kind of immature haemopoietic cells. I agree with Geschickter and Copeland and Churg and Gordon that in cases in which the nature of the cells is uncertain, it is best to admit this and to speak of them simply as myeloma cells: they are probably only immature forms or variants of the more typical plasma cells of the majority of cases of myelomatosis.

Cappell's findings in his Case 1 of transition forms between plasma cells and myeloblasts and in his Case 2 of possible transitions between myeloma cells and fibre producing cells are of significance, suggesting that myeloma plasma cells are but variant derivatives of undifferentiated reticulum cells which also have granulocytic and fibroblastic potencies as well. This does not conflict with the customary view, based mainly on studies of chronic inflammatory lesions that plasma cells are related to lymphocytes, for lymphocytes also occur in bone marrow, and arise here from the same stem-cells as the myeloblasts and erythroblasts and all other constituents of the bone marrow. The fact that plasma cell tumours usually arise in bone marrow and do not occur primarily in lymph glands is certainly of interest as regards the histogenesis of plasma cells.

The multinucleated cells of plasma-celled and other myelomas are of no special histogenetic significance except for their multiple nuclei: they are similar in structure to the other cells in the tumours. The suggestion that they represent megakaryocytes as in Gunn and Mahle's title 'megakaryoblastic myeloma' is unwarranted.

justified, because the prognosis of solitary plasmacytoma following adequate surgical or radiation treatment is good. The radiographic appearances of plasmacytoma are not characteristic and do not enable it to be distinguished from endosteal sarcoma, giant cell tumour or metastatic growth. The urine of a patient with supposedly solitary plasmacytoma of bone should be examined repeatedly for Bence Jones proteose, its presence must be looked upon as clear evidence of extensive involvement of bone marrow, in spite of negative radiographic findings. If thorough radiographic examination a year or more from the date of tentative diagnosis is unequivocally negative and proteosuria has been regularly absent, it is improbable that signs of generalized myelomatosis will appear later and the tumour may be diagnosed with reasonable certainty as a solitary one. That a considerable number of such cases has now been reported suggests that there is a distinct entity, solitary plasmacytoma, which is not merely a precocious lesion of the 'system' disease myelomatosis.

PRIMARY PLASMOCYTOMA OF SOFT TISSUES

The rare primary plasma cell tumours of soft tissues are almost restricted to the mucous membranes and submucous tissues of the alimentary and respiratory passages of the head and neck, the most frequent sites being the nasal cavity and nasopharynx (Claiborn and Ferris, Blacklock and Macartney, Stewart and Taylor, Hellwig). Kaufmann refers also to plasmacytomas of the buccal cavity, tonsil, larynx and conjunctiva. These tumours form single or multiple polypoid or lobulated masses projecting into the neighbouring cavities and sometimes invading the underlying bones. In spite of this latter property, they are usually relatively benign, growing slowly and amenable to local removal or radiation therapy. Sometimes however, a plasmacytoma in this region invades the bones so extensively that it is difficult to decide whether the growth arose primarily in the mucous membranes or the bones, as in Stewart and Taylor's second case and in the remarkable case reported by Cappell and Mathers. In occasional cases secondary deposits have been present in the cervical lymph glands or else where (McNamara and Rogers). As Claiborn and Ferris pointed out, it is possible that some of the more malignant nasopharyngeal plasmacytomas may really have been secondary deposits from disseminated myelomatosis.

Gordon and Walker reported a case of well circumscribed plasmacytoma of the lung which was treated successfully by lobectomy.

REFERENCES

- Aputz K (1940) *Virchows Arch* 306 631
 Armstrong E, Faulds J S and Stewart M J (1946) *J Path Bact* 58 243
 Batts M (1939) *Arch Surg* 39 807
 Bell E T (1933) *Amer J Path* 9 393
 Blacklock J W S and Macartney C (1932) *J Path Bact*, 35 69
 Cappell D F (1929) *J Path Bact*, 32 293
 Cappell D F and Mathers R P (1935) *J Laryng Otol* 50 340
 CHURG, J and GORDON A J (1942) 'Multiple myeloma with unusual visceral involvement' *Arch Path* 34 546 (Literature on visceral lesions)
 CLAIBORN, L. N., and FERRIS H W (1931) Plasma cell tumors of the nasal and nasopharyngeal mucosa *Arch Surg* 23 477

it is quite possible that these and ordinary non leukaemic myelomatosis are but variants of the larger group of neoplastic myeloses which includes also myeloid leukaemia

SOLITARY PLASMOCYTOMA OF BONE

Multiple myelomatosis sometimes first declares its presence by a single prominent tumour in bone and in occasional cases the appearance of this apparently solitary growth precedes that of multiple growths in other bones by a period of many months or even years (Cutler *et al*) But there also occur rare cases in which a large destructive tumour of bone proves to be a plasmocytoma and is not followed by tumours elsewhere in the skeleton but is cured by

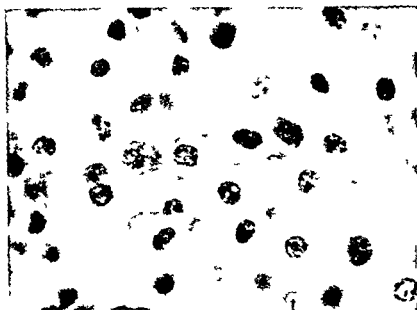


FIG 382—Section of solitary plasmocytoma of vertebra (Toluidine blue stain) ($\times 1200$)

amputation or irradiation For reports and reviews of these solitary plasma-cell tumours of bones see Stewart and Taylor and Willis In my paper I described a plasmocytoma of long duration in the second cervical vertebra of a man aged 45 (Fig 382) and reviewed 12 other acceptable cases of solitary growths in bones The 13 cases comprised 10 men and 3 women of ages ranging from 29 to 68 The bones involved were femur (5 cases usually upper third) vertebrae (3 cases) pelvis (2 cases) humerus (2 cases) and tibia (1 case) Involvement of a long bone was associated with pathological fracture in all but one of the cases

A correct clinical diagnosis of solitary plasmocytoma of bone can be reached only by (a) microscopical identification of the growth and (b) exclusion of the possibility that the tumour is merely the first sign of generalized myelomatosis (a) involves exploratory operation and (b) complete and repeated radiographical examination of the whole skeleton But, in a suspected case, these measures are

justified, because the prognosis of solitary plasmocytoma following adequate surgical or radiational treatment is good. The radiographic appearances of plasmocytoma are not characteristic and do not enable it to be distinguished from endosteal sarcoma, giant-cell tumour or metastatic growth. The urine of a patient with supposedly solitary plasmocytoma of bone should be examined repeatedly for Bence-Jones proteose its presence must be looked upon as clear evidence of extensive involvement of bone marrow, in spite of negative radiographic findings. If thorough radiographic examination a year or more from the date of tentative diagnosis is unequivocally negative and proteosuria has been regularly absent, it is improbable that signs of generalized myelomatosis will appear later and the tumour may be diagnosed with reasonable certainty as a solitary one. That a considerable number of such cases has now been reported suggests that there is a distinct entity solitary plasmocytoma which is not merely a precocious lesion of the system 'disease myelomatosis'.

PRIMARY PLASMOCYTOMA OF SOFT TISSUES

The rare primary plasma cell tumours of soft tissues are almost restricted to the mucous membranes and submucous tissues of the alimentary and respiratory passages of the head and neck, the most frequent sites being the nasal cavity and nasopharynx (Claiborn and Ferris, Blacklock and Macartney, Stewart and Taylor, Hellwig). Kaufmann refers also to plasmocytomas of the buccal cavity, tonsil, larynx and conjunctiva. These tumours form single or multiple polypoid or lobulated masses projecting into the neighbouring cavities and sometimes invading the underlying bones. In spite of this latter property, they are usually relatively benign, growing slowly and amenable to local removal or radiation therapy. Sometimes, however, a plasmocytoma in this region invades the bones so extensively that it is difficult to decide whether the growth arose primarily in the mucous membranes or the bones, as in Stewart and Taylor's second case and in the remarkable case reported by Cappell and Mathers. In occasional cases secondary deposits have been present in the cervical lymph glands or else where (McNamara and Rogers). As Claiborn and Ferris pointed out, it is possible that some of the more malignant nasopharyngeal plasmocytomas may really have been secondary deposits from disseminated myelomatosis.

Gordon and Walker reported a case of well circumscribed plasmocytoma of the lung which was treated successfully by lobectomy.

REFERENCES

- Apitz K. (1940) *Virchows Arch* 306 631
 Armstrong E, Faulds J S and Stewart M J (1946) *J Path Bact* 58 243
 Batts M (1939) *Arch Surg* 39 807
 Bell E T (1933) *Amer J Path*, 9 393
 Blacklock J W S and Macartney C (1932) *J Path Bact* 35 69
 Cappell D F (1929) *J Path Bact* 32 293
 Cappell D F and Mathers R P (1935) *J Laryng Otol*, 50 340
 CHURCH, J., and GORDON A J (1942) Multiple myeloma with unusual visceral involvement *Arch Path* 34 546 (Literature on visceral lesions)
 CLAIBORN, L N., and FERRIS, H W (1931) Plasma cell tumors of the nasal and nasopharyngeal mucosa *Arch Surg* 23 477

- Cosin L (1935) *Brit J Surg* 23 110
- CUTLER, M BUSCHKE F, and CANTRIL, S T (1936) The course of single myeloma of bone *Surg Gyn Obst* 62 918
- GESCHICKTER C F and COPELAND, M M (1928) Multiple myeloma *Arch Surg* 16 807 (A useful review with chronological reference list)
- Gordon J and Walker G (1944) *Arch Path* 37 222
- Gunn F D and Mahle A E (1938) *Arch Path* 26 377
- Hellwig C A (1943) *Arch Path* 36 95
- Kaufmann E (1929) *Pathology* (Reimann's translation) Philadelphia
- Lohlein M (1921) *Beitr path Anat* 69 295
- McNamara W L and Rogers R J (1943) *Arch Path* 36 89
- Newns G R and Edwards J L (1944) *J Path Bact* 56 259
- Randall O S (1933) *Amer J Cancer* 19 838
- STEWART, M J, and TAYLOR, A L (1932) Observations on solitary plasmacytoma , *J Path Bact* 35 541
- Wallgren A (1921) *Virchows Arch* 232 381
- Willis R A (1930) *J Coll Surg Austral* 3 295
- Willis R A (1938) *Med J Austral* 11 717
- WILLIS R A (1941) Solitary plasmacytoma of bone *J Path Bact* 53 77 (Case report and review)

CHAPTER 51

OTHER NEOPLASMS OF HAEMOPOIETIC TISSUES

IN THE preceding two chapters we have discussed tumours of lymphoid tissues and plasma cell tumours. The following neoplastic diseases of haemopoietic tissues remain for brief consideration

- 1 Myelogenous leukaemia
- 2 Chloroma
- 3 Polycythaemia vera
- 4 Basophil cell tumours
- 5 Monocytic leukaemia "

MYELOGENOUS LEUKAEMIA

Myelogenous leukaemia is but the over-population of the blood stream by malignant leucocytes following neoplastic change in the granulocytic series of cells in the bone marrow. This view, the truth of which is evident alike from the distribution of lesions, the cytology of the disease, its lethality, and the analogy with lymphoid tumours and leukaemias is now all but universally accepted. Israels (1940) is one of the few modern workers who regard leukaemias as non neoplastic. He bases this opinion on the normal development *in vitro* of leucocytes from the marrow of leukaemic patients, but it is noteworthy that none of his patients came to necropsy, and that their leucocyte counts were all low, lying between 14 000 and 32 000 cells per cubic millimetre. Were the cells he depicts really leukaemic cells? And even if they were, why should neoplastic leukaemic cells not show maturation changes approaching the normal? Many tumours show nearly normal cellular differentiation.

It is unnecessary here to describe the clinical and pathological characters of the disease in detail, these are given in many text books and in Forkner's monograph. Certain special features only are selected for comment here.

(1) Mode of origin

As with lymphoid tumours so with myeloid ones, the extent of the area of tissue suffering neoplastic change is difficult to determine. Does this take place in a restricted region of bone marrow or as a widespread system disease of much or all of this tissue? The answer is even more difficult to give than for lymphoid tissues for full examination of the bone marrow is seldom possible until late stages of the disease, when the extent of the primary lesions is obscured by almost universal secondary dissemination and infiltration.

Diffuse invasive extension from the primary neoplastic areas and from metastatic colonies of leukaemic cells must speedily obliterate all evidence of the original extent of those primary areas. That dissemination plays a great part is shown by the widespread diffuse leukaemic infiltrates in many non haemopoietic tissues.

- Cosin L (1935) *Brit J Surg* 23 110
- CUTLER M, BUSCHKE, F, and CANTRIL, S T (1936) The course of single myeloma of bone *Surg Gyn Obst* 62 918
- GESCHICKTER C F and COPELAND, M M (1928) Multiple myeloma *Arch Surg* 16 807 (A useful review with chronological reference list)
- Gordon J and Walker G (1944) *Arch Path* 37 222
- Gunn F D and Mahle A E (1938) *Arch Path* 26 377
- Hellwig C A (1943) *Arch Path* 36 95
- Kaufmann E (1929) *Pathology* (Reimann's translation) Philadelphia
- Lohlein M (1921) *Beitr path Anat* 69 295
- McNamara W L and Rogers R J (1943) *Arch Path* 36 89
- News G R and Edwards J L (1944) *J Path Bact* 56 259
- Randall O S (1933) *Amer J Cancer* 19 838
- STEWART, M J, and TAYLOR A L (1932) Observations on solitary plasmacytoma, *J Path Bact* 35 541
- Wallgren A (1921) *Virchows Arch* 232 381
- Willis R A (1930) *J Coll Surg Austral* 3 295
- Willis R A (1938) *Med J Austral* 11 717
- WILLIS R A (1941) Solitary plasmacytoma of bone *J Path Bact* 53 77 (Case report and review)

occur in the liver, spleen and bone marrow itself. They are probably responsible for the bulk of the leukaemic deposits in the liver and spleen, in which the occurrence of autochthonous leukaemic change is, I think, very improbable.

(2) Age and sex

The more usual form, the chronic form, of myelogenous leukaemia is rare in patients under 30 years of age—most cases are in the fourth and fifth decades. But acute leukaemias, many of which are myelogenous, are commonest in young people, according to Warren they occur at three distinct periods, namely, 24 per cent before the age of 10, 42 per cent between 25 and 35, and 20 per cent between 45 and 50. Kelsey and Anderson reported a case of congenital myeloid leukaemia and reviewed 9 other recorded cases of congenital leukaemia, of

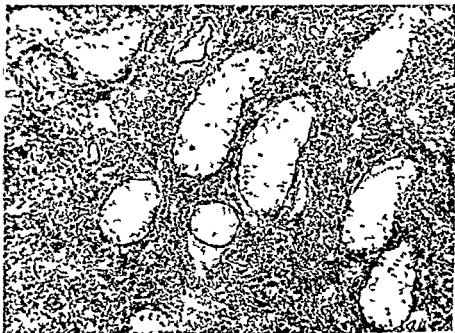


FIG. 385.—Testis from a man of 48 years showing severe myelogenous leukaemic infiltration ($\times 100$)

which 8 were myeloid. It is important not to mistake the blood picture of erythroblastosis foetalis for leukaemia. Both chronic and acute myeloid leukaemias affect males about twice as frequently as females.

(3) Cytology

The circulating cells in myelogenous leukaemia are not merely immature cells, but are often structurally atypical, defying identification as 'myelocytes', 'metamyelocytes', 'myeloblasts', etc. In many cases of leukaemia precise differential counts are impossible. In the more acute forms of the disease mitotic figures are often seen in the cells in blood films (Bowcock, other references by Forkner, and see Fig. 386). The relative proportions of cells with neutrophil, eosinophil and basophil granules vary greatly, cases with great predominance of eosinophil or basophil granulocytes justifying the titles 'eosinophil cell leukaemia' and 'basophil cell leukaemia' are rare (Forkner, Lillie) and caution

such as lungs skin kidneys and testes (Figs 383-385) These infiltrates are certainly due to metastatic colonization of the tissues by malignant leucocytes

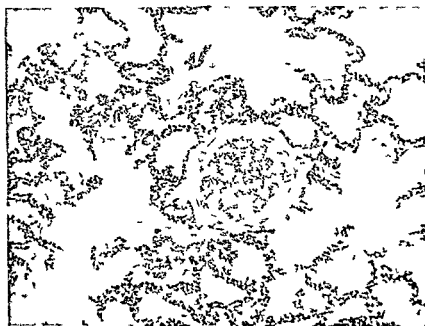


FIG 383 —Lung from a man of 43 years with severe myelogenous leukaemia whose leucocyte count exceeded 1 000 000 per cubic millimetre showing a blood vessel packed with leukaemic cells and heavy infiltration of the lung septa ($\times 80$)

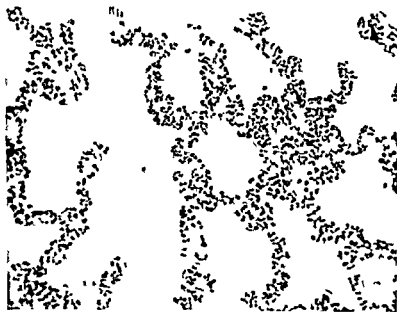


FIG 384 —Detail of lung septa in Fig 383 ($\times 150$)

brought there by the blood stream and *not* as was once supposed to autochthonous extra medullary leucopoiesis. Similar metastatic infiltrates must also

lobulated nuclei as 'megakaryocytes'. It is, however, doubtful if these large cells are indeed megakaryocytes, the resemblance amounts to no more than multinucleation or nuclear lobulation and it must not be overlooked that large multinucleated cells may appear in hyperplastic spleen or lymph glands in other pathological conditions not involving "myeloid transformation", as in the peculiar lesion described by Collins. Neither the giant cells of Hodgkin's disease nor the multinucleated cells of myelomatosis are megakaryocytes, but large tumour cells of the kind composing the tumour. May not multinucleated tumour cells appear also in myelogenous leukaemia? Or may not some of the multinucleated cells in the leukaemic spleen be merely hyperplastic, perhaps phagocytic, reticular cells evoked by the presence of the pathological leucocytes? I do not deny that myeloid metaplasia may possibly occur, but I think the question needs further study with the foregoing possibilities in mind.

(7) Myeloid leukaemia in animals

Myeloid leukaemia occurs in dogs, cattle, horses, mice, rats and probably other mammals, and in birds (Furth *et al*, Forkner, Feldman, Wilens and Sproul). Lillie reported leukaemia with predominance of basophil myelocytes in a cat.

(8) Causation of myelogenous leukaemia

Hueper's book (1942, Chapter VI) contains a good review of leukaemia or leukaemoid reactions occurring in persons exposed to benzol, X rays or radio active substances, and in experimental animals treated by benzol, indole, carcinogenic hydrocarbons and other substances, or exposed to radiation. Because of the difficulty of distinguishing true leukaemic from leukaemoid blood pictures in some cases, and because the number of reported cases of leukaemia in suspected occupations is still small, the evidence that human leukaemia is caused by extrinsic agents is still inconclusive. But it is at least strongly suggestive, and fully justifies Hueper's recommendation of a 'diligent search in the occupational history of every leukaemic patient for evidence of a prolonged contact with chemical agents affecting leucopoiesis'. Many occupations involve close contact with benzene, trinitrotoluene or other volatile organic substances which may damage the leucopoietic tissues, and all drugs or other substances known to be capable of causing agranulocytosis should also be suspect as possible causes of leukaemia.

CHLOROMA

Forkner (1938) gives a good account of *chloroma* and *chloroleukaemia*. These rare greenish nodular or diffuse growths may occur in any soft tissues but have a special predilection for periosteum. They consist of rounded poorly differentiated actively multiplying cells usually of uniform size and with single spherical nuclei. Earlier writers identified the cells as lymphoblastic in some cases and myeloblastic in others, but there is now little doubt that all chloromas are myeloblastic and that they constitute merely one variant of myelogenous leukaemic metastasis or infiltration. With few exceptions the patients are children or adolescents, have frankly leukaemic blood changes, but these may be overlooked because

is needed not to make a false diagnosis of the former in cases of great eosinophilia from other diseases such as parasitic infections Hodgkin's disease or occasional carcinomas with eosinophilia

(4) Leukanaemia"

This name is applied to those rare cases in which pernicious anaemia or a pernicious anaemia like blood picture has been followed by the development of myelogenous leukaemia (Forkner Foy *et al*)

(5) "Erythroleukaemia

This name refers to cases of associated erythrocythaemia and myelogenous leukaemia either coexisting or the latter supervening on the former. Many cases of this kind have been recorded (Weber, Forkner and see Case II below), the

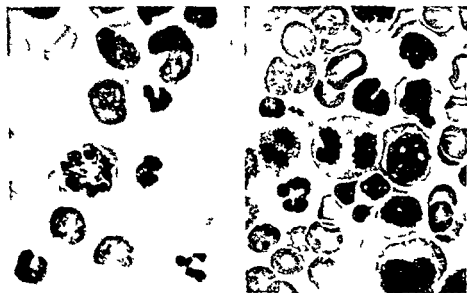


FIG. 386—Mitoses in a blood film from a case of myelogenous leukaemia ($\times 1000$)

association is too frequent to be purely fortuitous and some aetiological relationship between the two conditions must exist. Perhaps this relationship is that both diseases are neoplastic and that neoplastic change initially affecting the erythropoietic series of cells may later extend to the leucopoietic

(6) 'Myeloid transformation' of the spleen or other tissues

Huge enlargement of the spleen occurs in many cases of chronic myelogenous leukaemia—whence the clinical designation 'splenomedullary leukaemia'. Microscopically the enlargement is seen to be due mainly to great accumulation of leukaemic cells often along with some giant cells and it has been debated whether these have arisen from arrested blood borne cells or from myeloid transformation of splenic tissue. Although proof one way or the other may be difficult or impossible the former explanation namely that the splenic disease is essentially metastatic seems to me to be much the more likely. Upholders of the 'myeloid transformation' hypothesis have identified the large cells with multiple or

In all respects these cells resemble immature nucleated cells of the erythroblastic series. Mitotic figures are rare. The multinucleated cells vary in size, shape and number of



FIG 387—*Case II* Malignant erythroblastoma ($\times 150$)

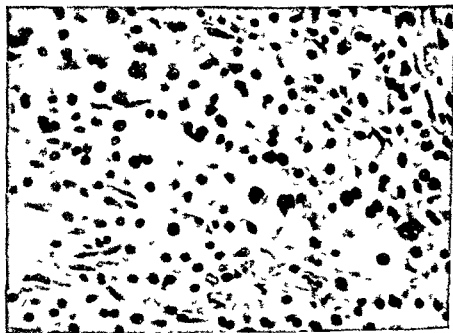


FIG 388—Detail of Fig 387 ($\times 500$)

nuclei the largest attain diameters of 50μ or more and contain 10 to 20 nuclei in a section usually situated in a concentric zone about midway between the centre and periphery of the cell. The cytoplasm of the large cells is homogeneous and eosinophilic.

attention is often focused on a clinically obtrusive tumour of the skull, spine or some other part. In most cases the disease runs an acute course and proves fatal within a few weeks or months. Chronic cases are rare. The green colour of the tumours fades on exposure to oxygen but may be restored by hydrogen peroxide. Feldman gives references to chloroma in pigs and cattle and Wilens and Sproul saw conspicuous examples in leukaemic rats.

The following case exemplifies chloromatous infiltrations accompanying other wise ordinary myelogenous leukaemia.

Case I—Male aged 25 was under treatment for some months for typical myelogenous leukaemia the leucocyte count reaching 300 000 per cubic millimetre and showing a high proportion of immature cells. *Necropsy*—Liver $7\frac{1}{2}$ pounds pale and mottled contains one greenish tumour 1.5 centimetres in diameter. Spleen $17\frac{1}{2}$ pounds pink with dusky greenish patches. Lymph glands moderately enlarged soft green. Left spermatic cord thickened by greenish infiltration. Skeleton bone marrow of vertebrae and femur greenish skull normal other bones not sectioned. Other organs show pallor only. On exposure to air for half hour green colour of tissues had faded. *Histology*—Typical myeloid leukaemic infiltrations with focal tumour like aggregations in places.

From my department Laurie described an unusual case of chloroma with well defined metastatic plaques on the dura mater. In another case on which I performed the necropsy there were extensive paravertebral lesions with paraplegia and the patient had been operated on for 'spinal tumour'.

POLYCYTHAEMIA VERA OR ERYTHRAEMIA

For clinical and pathological details of this disease consult Weber's excellent monograph (1921). All that is intended here is to express agreement with Weber's view (1936) that this disease is probably 'a primary neoplastic process in the erythroblastic portion of the bone marrow analogous to myelosis (myeloid leukaemia) in the leucoblastic portion'. This view is supported by the more than fortuitous association of erythraemia and leukaemia already referred to and by cases like the following in which a malignant haemopoietic (almost certainly erythropoietic) neoplasm without leukaemia supervened on polycythemia.

Case II—History—In 1929 a man aged 31 attended hospital because of haemoptysis and was found to have splenomegaly red-cell count 8 850 000 and Hb 130 per cent. Treated by X rays and phenylhydrazine he remained fairly well but continued to have attacks of haemoptysis. In 1940 red-cell count was 8 500 000 and Hb 140 per cent. Late in 1942 he began to lose weight and strength and his colour rapidly changed from purple to pale. In January 1943 red-cell count was 4 million Hb 55 per cent white cell count 12 500 (62 per cent neutrophils 30.5 per cent lymphocytes). Patient died in February at age of 45 years. *Necropsy*—Liver enlarged pale and mottled spleen $4\frac{1}{2}$ pounds pale red mottled with white areas. Kidneys contain ill-defined white areas. Lymph glands all appear normal. Vertebrae and ribs contain many irregular areas of white growth replacing marrow and forming smoothly rounded subperiosteal swellings up to 1 centimetre deep. Skull normal but dura mater of left middle fossa contains a projecting plaque of soft white growth 3 centimetres in diameter. *Histology* (Figs 387-389)—Dural skeletal and renal growths consist of mingled mononucleated round and multinucleated giant cells with all intermediate forms. The mononucleated cells predominate they are well defined average about 10μ in diameter contain dense darkly stained spherical nuclei about 6μ in average diameter and their homogeneous cytoplasm is distinctly eosinophilic in most cells but faintly basophilic or polychromatic in others.

diameter about 15μ with single rounded or reniform nuclei and cytoplasm densely studded with fine strongly basophil granules similar to those of next case

Case IV—For some months a slowly enlarging soft pendulous tumour of the scrotum had been noticed in a male English setter aged 12. The dog was destroyed and the tumour removed but the viscera were not examined. The tumour measured 5 centimetres in diameter was unconnected with the testes and arose from the scrotal wall. It consisted of pliable tissue resembling mingled soft fibrous and adipose tissue, and was clothed by thin skin. *Histology*—Similar to previous case but tissues more heavily



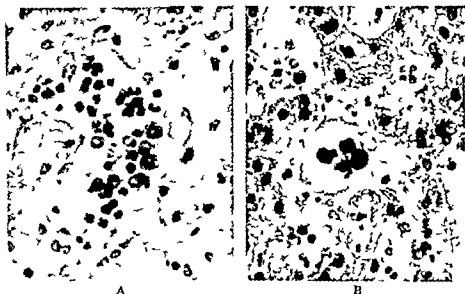
FIG. 390—*Case II*. Basophil-cell tumour from a dog (Inset slightly retouched) ($\times 100$ and $\times 500$)

infiltrated by the basophil granular cells which were fully studied by Leishman and Giemsa stains also (Fig. 390)

MONOCYTIC LEUKAEMIA

Cases of monocytic leukaemia have been described and reviewed by Dameschek Clough Campbell *et al*, and Forkner. Some workers, e.g. Forkner think this disease is an entity distinct from other kinds of leukaemia, others with whom I ally myself contest this and believe that "monocytic" leukaemia is usually myeloid leukaemia with monocytoïd myeloblasts or with reversible monocytosis (Naegeli), or that it is only a variant of lymphatic leukaemia (W. L. To me as to Gulland and Goodall the monocyte is not a distinct species of cell but only a variant of the whole lymphocyte mononuclear series, and in blood films all transitions can be traced between "typical" lymphocytes and typical monocytes. This opinion has been strengthened by my examination of blood films from several cases of supposed "monocytic" leukaemia and by perusal of reported cases, most of these seem to me to be indistinguishable from the

Transition forms between the small and large cells are plentiful. Spleen shows patches and diffuse infiltrations of similar cells, so also do some lymph glands. Liver shows many small intravascular foci of mononucleated cells resembling erythropoietic foci and the sinusoids contain also many syncytial masses with large irregular darkly stained homogeneous masses of chromatin (Fig 389). *Comment*—The morphology of the tumour cells shows almost conclusively that they are abnormal pleomorphic cells of the erythroblastic series. I interpret the case as one of true polycythaemia terminating in malignant erythroblastoma with disseminated metastatic lesions in liver, spleen, lymph glands, kidneys, dura mater and possibly in the bones also; the condition is the erythroblastic analogue of myeloid leukaemia with metastatic tumours and infiltrations. There was no sign of maturation of the tumour cells to form erythrocytes. Perhaps *pari passu* with the enhanced malignancy of erythropoietic growth, the capacity to mature was lost, this change corresponding with the sudden clinical change from simple (benign)



A

B

FIG 389—Case II. The liver. A = an erythropoietic focus in a sinusoid. B = a syncytial mass in a sinusoid. ($\times 500$)

polycythaemia to the non-polycythaemic state. As Parkes Weber suggests, polycythaemia may be regarded as a relatively benign neoplasm; the foregoing case illustrates its more malignant counterpart.

BASOPHIL CELL TUMOURS

Excessive numbers of basophil granulocytes may be seen in myelogenous leukaemia, but I know of no records of localized basophil cell tumours in man. Rudduck and I studied the following two instances of such tumours in dogs.

Case III—For 4 years a male pug dog aged 14 had had slowly enlarging soft pendulous tumours of the skin of the neck, chest and perineum; the animal was destroyed. *Necropsy*—No visceral lesions were found. The 3 largest skin tumours measured 10.5 and 4 centimetres in their main diameters; there were several smaller tumours also. These all consisted of lax, finely spongy fibrous-looking tissue, not encapsulated but clothed by thin intact skin. *Histology*—Dermal and subcutaneous tissues show marked general increase of connective tissues and many new formed blood vessels. These tissues are lightly or heavily infiltrated throughout by darkly stained rounded cells of average

CHAPTER 52

THE GLIOMATA

IN THE strict sense glioma means a tumour of neuroglial tissue, i.e. the non mesenchymal stromal tissue of the central nervous system. The term includes the astrocytes, oligodendrocytes and ependyma, gliomas are not derived from and composed of cells of these types. The term is however commonly extended to embrace three other kinds of growth not derived from ordinary neuroglial tissues—medulloblastoma and neuro-epithelioma, tumours of embryonic nervous tissue, and pinealoma. 'Glioma' should be used to include ganglioneuromas of the central nervous system (if these ever occur—see Chapter 55) tumours of the choroid plexuses (Choroid plexus papilloma) or tumours of the mesenchymal tissues of the nervous system or its sheath. The view espoused by many French workers that these last named tumours are of neuro-ectodermal origin and the corresponding practice of designating them as gliomas and nerve-sheath tumours peripheral gliomas cause needless confusion.

As I am sceptical of the value of complicated sub-divisions of the gliomas and hold seemingly over-simplified views regarding their histogenesis and histology it is necessary to state briefly the extent of the material from which those views were derived. At the Alfred Hospital Melbourne from 1930 to 1940 I had the good fortune to be closely associated with Mr H. C. Trumble's active neuro-surgical clinic and to carry out in collaboration with Dr L. B. Cox a careful microscopical study of nearly 300 surgical biopsy specimens of gliomas and of 136 necropsies of cases of primary intracranial tumours including 84 gliomas. In the microscopical study of nearly 100 specimens in the early part of the series we employed not only the more usual stains but also the metallic impregnation methods of Cajal, Hortega and Bielschowsky with which Cox made many beautiful preparations described in an important paper by him in 1933. Then after however these special methods were used less and less for we became increasingly convinced that they are much less specific than is often assumed and that in tumours of doubtful nature their results are often difficult to interpret and that in only occasional cases did they yield definite and helpful information not obtainable by the more usual staining methods.

of lymphatic leukaemia and to be monocytic only in that the appearances of some or many of the abnormal cells resemble those arbitrarily accepted as 'typical' of monocytes

REFERENCES

- Bowcock H (1932) *Arch Int Med* 50 908
 Campbell A C P Henderson J L and Croom J H (1936) *J Path Bact* 42 617
 Clough P W (1932) *Bull Johns Hopkins Hosp* 51 148
 Collins D H (1933) *J Path Bact* 37 123
 Dameschek W (1930) *Arch Int Med* 46 718
 Feldman W H (1932) *Neoplasms of Domesticated Animals* Philadelphia
 Forkner C E (1937) *Arch Int Med* 60 582
 Forkner C E (1938) *Leukemia and Allied Disorders* New York
 Foy H Athena Kondi and Murray J F (1946) *J Path Bact* 58 157
 Furth J Ferris H W and Reznikoff P (1935) *J Am r Med Assoc* 105 1824
 Gulland G L and Goodall A (1925) *The Blood* Edinburgh
 Hueper W C (1942) *Occupational Tumors and Allied Diseases* Springfield
 Israels M C G (1940) *J Path Bact* 51 235
 Kelsey W M and Anderson D H (1939) *Amer J Dis Child* 58 1268
 Laurie H W S (1937) *Med J Austral* i 753
 Lilhe R D (1931) *Amer J Path* 7 713
 NAUGELI O (1931) *Blutkrankheiten und Blutdiagnostik* Berlin (An invaluable reference book)
 Warren S L (1929) *Amer J Med Sci* 178 490
 WEBER F P (1921) *Polycythaemia Erythrocytosis and Erythraemia (Vaquez, Osler Disease)* London (An excellent monograph)
 Weber F P (1936) *Endocrine Tumours and Other Essays* p 101 London
 White E (1941) *Med J Austral* ii 167
 Wilens S L and Sproul E E (1936) *Amer J Path* 12 249

poorly differentiated cells ("glioblastomas") often show areas of recognizable tumour astrocytes. Indeed the frequent presence of such areas makes it clear that most 'glioblastomas' are anaplastic astrocytomas. It is highly probable that they all are, but it is not possible to affirm this, since some of them are completely anaplastic and lack all signs of differentiation. A further objection to the '-blastoma' terminations has already been mentioned namely, their embryological implication. 'Astroblastomas' and 'spongioblastomas' are not, as the names imply, tumours of immature embryonic cells but anaplastic tumours derived from adult tissues. It is particularly important to avoid this false implication of an embryonic origin, since there is a glioma the medulloblastoma, which is truly embryonic.

(d) The growth patterns of gliomas are unsafe grounds for creating sub divisions

The patterns of gliomas are partly determined by their intrinsic habits of growth and partly by the pattern of the invaded tissues. Scherer (1938) has emphasized this point and has shown that gliomas of intrinsically homogenous arrangement assume different patterns in grey and white matter, and that prominent perivascular or fascicular arrangement is often determined more by the pattern of the pre existing structures than by the habit of growth of the tumour cells themselves. It is therefore unsafe to use growth patterns or the shapes of the cells as bases of classification. In one area an astrocytoma may consist of plump asteroid cells devoid of polarity in another area of bundles of compressed fusiform cells and in another of elongated cells arranged radially around blood vessels. Tumour astrocytes or their anaplastic derivatives vary greatly in size and shape, they may be stellate fusiform, pyriform or multiform, they may be arranged loosely, compactly, in broad or narrow strands or in perivascular mantles but they are all still astrocytes. Cox fully described the great variations in shape of tumour astrocytes according to their positions and state of health. It is clear that Bailey and Cushing's 'spongioblastoma unipolare' (Penfield's 'polar spongioblastoma') is, as Cox suggested and as Russell and Bland proved by tissue culture, a fusiform celled or 'piloid' astrocytoma. And I have already expressed my conviction that the so called 'ependymal spongioblastoma' is often only an astrocytic glioma with prominent perivascular radial arrangement of elongated cells. Adjectives like 'multiforme', 'unipolare', 'piloid', 'giganto cellulare', 'fibrillar' and 'fascicular', used in naming gliomas have only a descriptive value and are of no significance as regards histogenesis and classification.

(e) Included cells of invaded tissues have often been misidentified as tumour cells

Cox made a special study of this subject and pointed out how the inclusion of nerve cells and fibres within gliomas or of non neoplastic astrocytes within medulloblastomas might lead to errors of interpretation and classification.

(f) The metallic impregnations are only relatively specific

This deserves repeated emphasis. It is true that typical normal astrocytes oligodendrocytes nerve cells and fibres or their well differentiated neoplastic counterparts, may show distinctive staining properties when appropriately fixed and treated. But it is also true, (i) that the metallic impregnations are often

the reduction of the number of sub-groups and names to the barest possible minimum

(a) *The three types of normal neuroglial cells are not sharply distinct*

Histologists recognize that while typical astrocytes and oligodendrocytes differ in form and staining properties, there are many transitional forms (Maximow and Bloom, 1944). Ependymal cells and immediately sub ependymal astrocytes are similar in cytoplasmic and nuclear structure and probably differ in form only because of their positions. Too much stress has been placed on the presence of blepharoplasten in ependymal cells, this relatively minor feature does not imply sharp distinction from sub ependymal cells.

(b) *The corresponding three types of gliomas are not sharply distinct*

While it is true that many gliomas consist mainly or wholly of cells with the typical forms and staining properties of astrocytes and a few gliomas consist of cells with the typical forms and staining properties of oligodendrocytes, many tumours contain both types of cells with transitions between them. Bailey and Bucy, Kwan and Alpers, and Cooper described transition forms between oligocytes and astrocytes in oligodendrogliomas, and Cooper particularly stressed the frequency of mixed 'oligo astrocytomas'. My own experience accords with Cooper's. I have seen more tumours of mixed or transitional structure than pure oligodendrogliomas. So also many of the tumours designated ependymomas are not sharply distinct from astrocytomas. Relatively few of these tumours have contained cavities lined by unmistakable ependyma; most of them have shown only a radiating arrangement of bipolar cells around blood vessels (Bailey and Cushing, Bailey 1932, Bailey, Buchanan and Bucy 1939) and these bipolar cells or so-called ependymal spongioblasts are often brilliantly impregnated by the gold sublimate method and show transitional forms between the simple polar shapes and undoubted astrocytes (Cox). My own findings accord with this and I agree with Cox's opinion that the 'ependymal spongioblast' is nearer in structure to the astrocytic series than to adult ependyma. Indeed, I doubt the validity of the terms ependymoblastoma, 'ependymal spongioblastoma' or 'ependymoma' applied to tumours of this kind; these names have often been uncritically applied to astrocytomas with prominent perivascular mantles of elongated cells. The only tumours unquestionably deserving the name 'ependymoma' are those with ependyma lined cavities and these are rare.

...ng degrees of and ... not mean distinct types of tumours

all differentiated
well differentiated
toma nor
or glioblast
they differ on
etc tumour
40) that
um

... called an astrocytoma. A
it not be called
spongio
cytic
ation
I agree
it most
entiated
posed of

(c) *Ependymoma*

In my opinion, the name should be applied only to tumours containing spaces lined by ependyma. Such tumours are rare.

(d) *Medulloblastoma* and *neuro epithelioma*

These are truly embryonic tumours arising from developmentally still immature nervous tissue, the former composed of diffuse masses of small embryonic cells, the latter (extremely rare) showing spaces lined by layers of embryonic neuro epithelium.

It is necessary to mention, in order to dismiss, two recently advanced hypotheses regarding the histogenesis of gliomas. One of these, put forward by Singer and Seiler (1933), is that the parenchyma of the gliomas is not neuroglial but neuronal and that their glial content is merely stromal. The other view, advanced by Globus and Kühlenbeck (1942) revives Cohnheim's embryonic cell rests and supposes gliomas to 'take origin from unripe neuroectodermal derivatives' and to undergo differentiation into "both neural and glial elements". Except in so far as medulloblastomas are embryonic tumours with therefore some latitude of potencies for differentiation neither of these hypotheses need be considered seriously: the simple neuroglial nature of the adult gliomas is beyond question. The writers cited and many others have mistaken altered astrocytes or included nerve cells for neoplastic nerve cells.

I commend to the reader Russell's 1939 paper as an excellent outline of the pathology of the gliomas and other intracranial tumours.

SEX, AGE AND SITE INCIDENCE OF GLIOMAS

(1) Sex

The sexes are nearly equally liable to gliomas. Males have predominated in some series, e.g. my necropsies were on 51 males and 33 females and Courville's collection of multiple gliomas comprised 77 males and 38 females. Medulloblastomas of the cerebellum appear to predominate in males (Bailey *et al*).

(2) Age

The age distribution curve for all gliomas (Bailey *et al*) shows two peaks, one in the second hemi-decade, the other in the fifth decade, with a trough in the later part of the second decade. The first peak is due to the frequency in young children of medulloblastomas and cerebellar astrocytomas, tumours which are relatively rare in later life. The peak in the fifth decade is due to the gradually increasing incidence of cerebral astrocytomas and "glioblastomas", which are common in adults but rare in children.

(3) Gliomas in children

Of 75 gliomas in children recorded by Bailey *et al*, 30 were classified as astrocytomas (the majority cerebellar); an additional 26 were in my opinion probably of astrocytic origin (7 "ependymomas", 10 "spongioblastomas", 7 "glioblastomas" and 2 "astroblastomas"), and 13 were medulloblastomas, nearly all cerebellar. The mean age of Bailey and Cushing's 25 cases of cerebellar medulloblastoma was 10 years. All 15 of their cerebellar astrocytomas were in young

fickle failing to impregnate the appropriate cells for no known reason or sporadically impregnating cells other than the appropriate ones (ii) that pathological tissues have seldom been subjected to standard treatment as regards the time elapsing between their removal and fixation the nature and purity of the fixatives used the time of fixation, and other unknown factors these being particularly relevant as regards necropsy and museum material and (iii) that tumour cells are tumour cells, manifesting varying degrees of anaplasia with abnormalities both of form and of staining properties For these reasons, when interpretation of the nature of a particular tumour is difficult from tissues stained by the ordinary methods interpretation of the metallic impregnation results is almost always more difficult still and it becomes merely a matter of arbitrary opinion as to which method to rely on most The following statement by Bailey *et al* (1939) in reference to several figures of neuroblastoma in his and Cushing's earlier monograph is significant 'On the basis of these silver impregnations, we classified two tumors as neuroblastomas, which we have since come to doubt The reduced silver method of Cajal is not specific even on normal tissue unless modified for each type of neurone which one wishes to demonstrate and used on tissue specially fixed for the method The Bielschowsky method is very unspecific under any circumstances' To which I would add that the multiplicity of the modifications of the metallic impregnation methods which have been and are used is clear evidence of their non specificity, and also a further source of endless confusion The most reliable of the metallic impregnations is Cajal's gold chloride sublimate method for astrocytes, but when it gives positive results, the astrocytic nature of the cells is seldom in doubt from preparations stained by the ordinary methods

The classification adopted

It will be clear that I do not favour rigid sub division of the gliomas But for descriptive purposes three main structural types corresponding to the three types of normal neuroglial tissue may be recognized to which must be added the truly embryonic tumours We thus have the following sub groups

(a) *Astrocytic glioma*

This group includes astrocytoma composed of well differentiated stellate cells astroblastoma composed of imperfectly differentiated stellate cells 'astrocytoma gigante cellulare' composed of large pleomorphic cells (often closely resembling nerve cells) spongioblastoma or glioblastoma multiforme composed mainly of pleomorphic poorly differentiated anaplastic cells most 'ependymal spongioblastomas' (the 'ependymoma' of most writers) composed of elongated cells arranged radially around vessels and fascicular forms of piloid astrocytoma composed of elongated cells arranged in bundles All of these are merely structural variants of a single species and several of them may be found in one tumour

(b) *Oligodendroglioma*

This name is appropriate for tumours composed wholly or predominantly of cells resembling oligodendrocytes They are not sharply distinct from astrocytic gliomas transitional or mixed tumours are common

(c) *Ependymoma*

In my opinion the name should be applied only to tumours containing spaces lined by ependyma. Such tumours are rare.

(d) *Medulloblastoma* and *neuro-epithelioma*

These are truly embryonic tumours arising from developmentally still immature nervous tissue, the former composed of diffuse masses of small embryonic cells, the latter (extremely rare) showing spaces lined by layers of embryonic neuro epithelium.

It is necessary to mention in order to dismiss, two recently advanced hypotheses regarding the histogenesis of gliomas. One of these, put forward by Singer and Seiler (1933) is that the parenchyma of the gliomas is not neuroglial but neuronic and that their glial content is merely stromal. The other view, advanced by Globus and Kuhlenbeck (1942), revives Cohnheim's embryonic cell rests and supposes gliomas to 'take origin from unripe neuroectodermal derivatives and to undergo differentiation into 'both neural and glial elements''. Except in so far as medulloblastomas are embryonic tumours with therefore some latitude of potencies for differentiation neither of these hypotheses need be considered seriously, the simple neuroglial nature of the adult gliomas is beyond question. The writers cited and many others have mistaken altered astrocytes or included nerve cells for neoplastic nerve cells.

I commend to the reader Russell's 1939 paper as an excellent outline of the pathology of the gliomas and other intracranial tumours.

SEX, AGE AND SITE INCIDENCE OF GLIOMAS

(1) Sex

The sexes are nearly equally liable to gliomas. Males have predominated in some series, e.g. my necropsies were on 51 males and 33 females and Courville's collection of multiple gliomas comprised 77 males and 38 females. Medulloblastomas of the cerebellum appear to predominate in males (Bailey *et al*).

(2) Age

The age distribution curve for all gliomas (Bailey *et al*) shows two peaks, one in the second hemi-decade, the other in the fifth decade, with a trough in the later part of the second decade. The first peak is due to the frequency in young children of medulloblastomas and cerebellar astrocytomas, tumours which are relatively rare in later life. The peak in the fifth decade is due to the gradually increasing incidence of cerebral astrocytomas and 'glioblastomas', which are common in adults but rare in children.

(3) Gliomas in children

Of 75 gliomas in children recorded by Bailey *et al*, 30 were classified as astrocytomas (the majority cerebellar), an additional 26 were in my opinion probably of astrocytic origin (7 "ependymomas", 10 'spongioblastomas', 7 'glioblastomas' and 2 'astroblastomas'), and 13 were medulloblastomas, nearly all cerebellar. The mean age of Bailey and Cushing's 25 cases of cerebellar medulloblastoma was 10 years. All 15 of their cerebellar astrocytomas were in young

people of mean age 13. The mean age of Bucy and Gustafson's 25 cases of cerebellar astrocytoma was 9 years, with a range from 21 months to 22 years. My 84 necropsy cases of glioma included 13 under the age of 20: the tumours were 7 medulloblastomas, 4 astrocytomas (3 in the cerebellum) and 2 diffuse cellular tumours of undetermined nature. Russell and Ellis reported a large "polar spongioblastoma" in the cerebrum of a still born full term foetus.

(4) Gliomas in adults

With infrequent exceptions these are astrocytic tumours of the cerebrum, cerebellar gliomas in adults are relatively infrequent. Poorly differentiated growths—multiform glioblastomas—rather outnumber well differentiated astrocytomas, but all transitions and combinations occur. The well differentiated astrocytomas occur on an average decidedly earlier than the more anaplastic growths: the former being most frequent in the third decade and the latter in the fourth and fifth decades. Oligodendrogliomas are almost restricted to adults. Bailey *et al* found only one example amongst 75 gliomas in children.

(5) Sites

The cerebellum and fourth ventricle are thus the commonest sites of gliomas in children: the cerebrum is the commonest site in adults. The brain stem is an infrequent site but appears to be relatively more often affected in children than in adults: when glioblastomas occur in children they are usually situated in the pons (Bailey *et al*). Gliomas of the spinal cord are uncommon but may be of any of the types seen in the brain. Kernohan *et al* depicted examples of ependymoma, spongioblastoma, "astroblastoma", astrocytoma, oligodendroglioma and medulloblastoma but gave no details of the cases. They noted the frequent association of spinal gliomas with syringomyelia. Cox (1937) also saw an intramedullary glioma associated with syringomyelia. Gliomas of the optic nerves or chiasma are rare tumours, least uncommon in children and young people (Verhoeff, Martin and Cushing, Bailey *et al*). I know of no acceptable report of glioma of the par nervosa of the pituitary gland. True astrocytic gliomas of the retina are described in Chapter 57.

(6) Multiple gliomas

These are not unusual. Courville reviewed 134 cases including 21 of his own and he estimated that multiple growths occur in about 8 per cent of cases of glioma. Most of the patients were adults: most of the tumours were in the cerebrum and multiplicity was more frequent with multiform glioblastomas than with astrocytomas—10 per cent and 6 per cent of cases respectively. In most cases 2 tumours were present but cases with 4 or 5 separate growths were observed. These were sometimes situated in one hemisphere, sometimes in both hemispheres, sometimes in one hemisphere and the corpus callosum. Needless to say careful dissection and microscopical study are necessary before concluding that two neighbouring growths are indeed distinct. My own series of 84 necropsies included 2 with certainly multiple gliomas—2 tumours in each case. With rare exceptions multiplicity cannot be explained by metastasis and is clearly due to multifocal origin.

(7) Diffuse gliomatosis

This is an appropriate name for those not unusual astrocytomas which diffusely affect extensive areas of the brain, their limits cannot be determined by the naked eye or even with the microscope. Nevin recorded good examples with excellent illustrations. The well differentiated tumour astrocytes, barely or not at all distinguishable from normal ones, are mingled intimately with the normal tissues, which show general swelling, pallor and blurred pattern but without losing their main structural markings or suffering any great change of consistency. Such tumours may affect a large part of one or both hemispheres.



FIG. 391.—Well differentiated astrocytoma of cerebrum of a woman of 47 years with 11 years history of fits. Successful removal of lobulated tumour 5 centimetres in diameter ($\times 150$)

Their diffuseness cannot be attributed wholly to proliferative invasion of the surrounding tissues, I agree with Scherer (1940) that they are 'primary diffuse neoplastic proliferations of the neuroglia of considerable areas of the brain'.

(8) Heterotopic gliomas

Heterotopic neuroglial tissue in the meninges has been observed by several workers (references by Bailey, 1936). Bailey described a meningeal astrocytoma presumably derived from such heterotopic tissue. Needless to say, in any case of this kind before the diagnosis of primary meningeal glioma or gliomatosis can be accepted as certain it must be shown that the brain and spinal cord contain no primary glioma to which the meningeal disease is secondary. Bratton and Robinson described two extra-cranial gliomatous tumours in infants, one of the palate and one of the subcutaneous tissues of the nose, the palatal tumour may have been a teratoma with predominant development of neural tissues but

people, of mean age 13. The mean age of Bucy and Gustafson's 25 cases of cerebellar astrocytoma was 9 years with a range from 21 months to 22 years. My 84 necropsy cases of glioma included 13 under the age of 20, the tumours were 7 medulloblastomas, 4 astrocytomas (3 in the cerebellum) and 2 diffuse cellular tumours of undetermined nature. Russell and Ellis reported a large 'polar' spongioblastoma in the cerebrum of a still born full term foetus.

(4) Gliomas in adults

With infrequent exceptions these are astrocytic tumours of the cerebrum. Cerebellar gliomas in adults are relatively infrequent. Poorly differentiated growths—multiform glioblastomas—rather outnumber well differentiated astrocytomas but all transitions and combinations occur. The well differentiated astrocytomas occur on an average decidedly earlier than the more anaplastic growths, the former being most frequent in the third decade and the latter in the fourth and fifth decades. Oligodendrogliomas are almost restricted to adults, Bailey *et al* found only one example amongst 75 gliomas in children.

(5) Sites

The cerebellum and fourth ventricle are thus the commonest sites of gliomas in children, the cerebrum is the commonest site in adults. The brain stem is an infrequent site but appears to be relatively more often affected in children than in adults when glioblastomas occur in children they are usually situated in the pons (Bailey *et al*). Gliomas of the spinal cord are uncommon but may be of any of the types seen in the brain. Kernohan *et al* depicted examples of 'ependymoma', spongioblastoma, 'astroblastoma', astrocytoma, oligodendroglioma and medulloblastoma but gave no details of the cases. They noted the frequent association of spinal gliomas with syringomyelia. Cox (1937) also saw an intramedullary glioma associated with syringomyelia. Gliomas of the optic nerves or chiasma are rare tumours, least uncommon in children and young people (Verhoeff, Martin and Cushing, Bailey *et al*). I know of no acceptable report of glioma of the par nervosa of the pituitary gland. True astrocytic gliomas of the retina are described in Chapter 57.

(6) Multiple gliomas

These are not unusual. Courville reviewed 134 cases including 21 of his own and he estimated that multiple growths occur in about 8 per cent of cases of glioma. Most of the patients were adults, most of the tumours were in the cerebrum and multiplicity was more frequent with 'multiform glioblastomas' than with astrocytomas—10 per cent and 6 per cent of cases respectively. In most cases 2 tumours were present but cases with 4 or 5 separate growths were observed. These were sometimes situated in one hemisphere, sometimes in both hemispheres, sometimes in one hemisphere and the corpus callosum. Needless to say careful dissection and microscopical study are necessary before concluding that two neighbouring growths are indeed distinct. My own series of 84 necropsies included 2 with certainly multiple gliomas—2 tumours in each case. With rare exceptions multiplicity cannot be explained by metastasis and is clearly due to multifocal origin.

descriptive adjectives like solid and cystic, circumscribed and diffuse, stellate celled and polar celled, while usefully applicable to particular tumours or to par

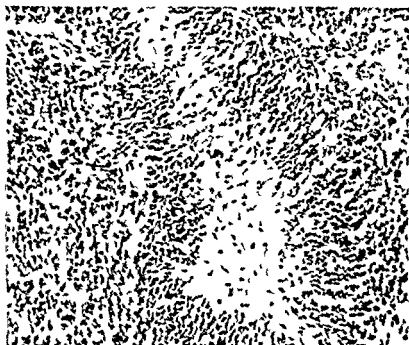


FIG. 393 —A well differentiated fibrous astrocytic area in a cellular glioblastoma of cerebrum of a man aged 35 ($\times 150$)

ticular parts of one tumour do not denote distinct types of growths. The "piloid" tumours are only a variety of conspicuously fibrillar astrocytoma with elongated

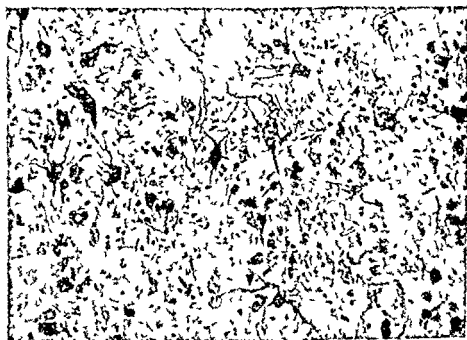


FIG. 394 —Tumour astrocytes in an astrocytomatous area of a cellular glioma of cerebrum (Cajal's gold-chloride sublimate method) ($\times 250$)

cells. Cox, Alpers and Rowe, Scherer and Bucy and Gustafson are amongst those who have stressed the diversity of cytology in the astrocytomas.

the nasal tumour consisted of astrocytic neuroglia only and was evidently derived from developmentally separated tissue

THE MAIN STRUCTURAL TYPES OF GLIOMA

I do not intend to repeat in detail the structural features of the commoner kinds of glioma. These have already been partly dealt with in the preceding discussion, they are illustrated in Figs 391 to 403, and full details and many other illustrations will be found in the various papers cited. Here will be given only a brief synopsis of each type with stress on some special points

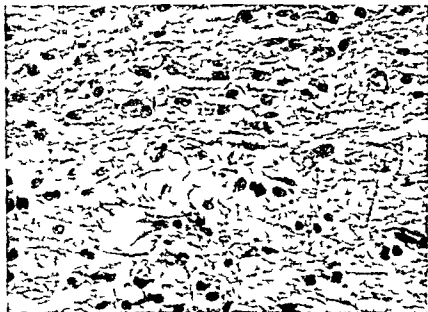


FIG 392 —Highly differentiated fibrous astrocytoma of pons of man of 43 years ($\times 400$)

(1) Astrocytic gliomas

Tumours of astrocytic origin constitute about three quarters of all gliomas. They show great diversity of structure and behaviour. This diversity justifies attempts to subdivide the group for practical prognostic purposes but it must be clearly recognized that the distinctions made are merely descriptive and utilitarian and not histogenetic. The most benign tumours of the group are the slowly growing circumscribed often cystic cerebellar astrocytomas of childhood the most malignant are the anaplastic pleomorphic-celled glioblastomas but all possible combinations and transitional forms of growth are encountered (See Figs 391-399)

Astrocytomas are composed mainly of well differentiated astrocytes stellate or elongated and of more or less abundant glial fibres. The distinction formerly made between protoplasmic and fibrillary astrocytomas is artificial and indeed pointless since all well differentiated astrocytic tumours contain glial fibres. Bailey *et al* (p 434) admitted that it would be better to say more fibrillary or less fibrillary thereby of course abrogating the distinction. So also

oligodendroglia to typical astrocytes can be found ' Cooper re emphasized this point

Calcification occurs in many oligodendrogliomas as in other brain tumours it usually commences around the blood vessels which often become mapped out prominently by their calcific sheaths

(3) Ependymomas

It will already be clear that in my opinion many of the tumours designated 'ependymoma' or 'ependymoblastoma' do not deserve that name but are merely one variety of elongate celled astrocytoma. The term ependymoma

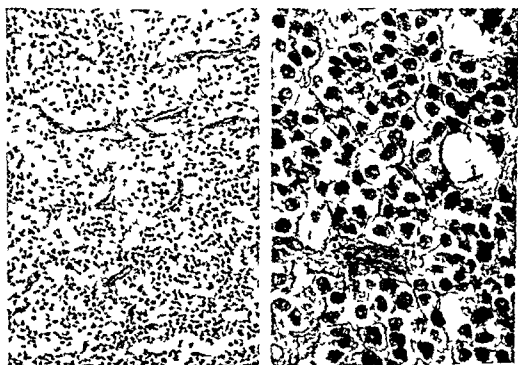


FIG. 400—Oligodendroglioma of cerebrum of man aged 46 ($\times 120$ and 400)

should be applied only to tumours in which spaces lined by unmistakable ependymal cells are present. As Russell (1939) has pointed out, not a few of the tumours reported as "neuro epitheliomas" with rosettes are really ependymomas with cavities lined by well differentiated, often ciliated ependymal cells. The ciliated cells arranged in rosettes show neuroglial processes and fibrils at their outer ends. True ependymomas are relatively benign slowly growing tumours. Their most usual sites are near the ventricles or in the spinal cord or filum terminale. One of Cox's specimens which I also examined, was of particular interest in that it consisted partly of ependyma lined lobules with cores of astrocytic tissue and partly of tissue with the structure of 'ependymoblastoma' composed of perivascular mantles of radiating elongated cells which, however had the typical staining properties of astrocytes. This tumour showed the close kinship of ependymal tumours and astrocytomas.

Two clinico pathological sub groups of the well differentiated astrocytomas may conveniently be recognized without, however, supposing a clear cut distinction

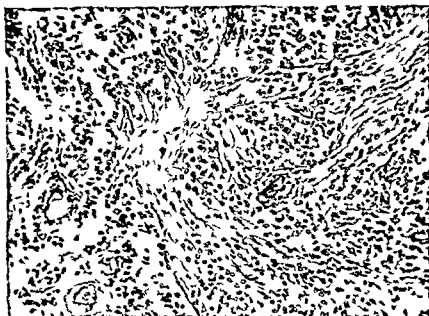


FIG 395 —Well differentiated fibrillary area in a cellular astrocytoma of cerebrum of a woman aged 23 ($\times 120$)

or any fundamental histogenetic difference. These are (i) well circumscribed benign astrocytomas usually in children usually cerebellar and usually cystic and (ii) poorly circumscribed infiltrating astrocytomas usually in adults usually

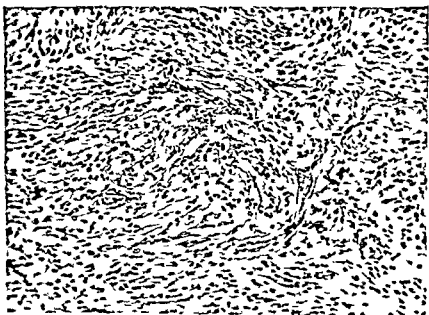


FIG 396 —Fusiform-celled fibrillary area in the same tumour as Fig 395 ($\times 120$)

cerebral and usually non-cystic. The benign cerebellar astrocytomas are well described by Bergstrand, Bucy and Gustafson and Bailey *et al*

not helpful in studying these small indifferent cells, which have been identified by some workers as neuroblasts and by others as spongioblasts. The elongated cells



FIG. 401—Rosettes in a diffusely cellular medulloblastoma of cerebellum of a boy aged 11 ($\times 200$)



FIG. 402—Diffuse spread of medulloblastoma in meninges. B = surface of brain. P = compact layer of tumour cells on pial surface. M = less compact tumour in sub arachnoid space ($\times 120$).

in some tumours have fine fibrillar processes, with staining properties like those of astrocytes, and there is little doubt that in the more slowly growing tumours

Kernohan *et al* stated that they had seen 6 tumours of the spinal cord containing canals lined by ependymal epithelium and their Fig 2 depicts two of these. But they gave no details of their cases, and their description of one of the growths as closely resembling choroid plexus with papillary epithelial structures containing cores of connective tissue does not suggest ependyma. Is it not possible that this tumour and perhaps others may have been metastases from unsuspected primary epithelial growths elsewhere?

I am not convinced of the identity of the tumours in some other reported cases of 'ependymoma', e.g. Cases 1 and 2 of Bailey *et al*. In such cases unless the whole tumour has been thoroughly studied the possibility of it having been a teratoma with plentiful neuro epithelial and ependymal components cannot be excluded. The younger the patient the greater is this possibility. An embryonic ependymoma if such ever occurs would be identical with neuro epithelioma (*see below*).

(4) Medulloblastomas

Medulloblastomas are far from rare, indeed in children they are only slightly less frequent than the cerebellar astrocytomas. Bailey (1932) recorded 55 medulloblastomas in a series of 378 gliomas from people of all ages. Earlier reports of these tumours referred to them as sarcomas of the cerebellum or meninges (references by Willis, 1934) but the descriptions enable us to identify many of these with confidence as medulloblastomas. Amongst the best recent accounts are those of Cairns and Russell, Wanke, and Bailey *et al*.

(a) Age site and sex incidence

Most of these tumours occur in infants or young children and their usual situation is in the vermis of the cerebellum or roof of the fourth ventricle. They are much less frequent in young adults and in the cerebrum. Bailey and Cushing recorded 25 cerebellar cases of mean age 10 years and 4 cerebral cases of mean age 36. Most medulloblastomas in adults are in young people. I have seen 3 cases of ages 25, 30 and 32. Bailey, Buchanan and Bucy reported 13 cases of cerebellar medulloblastoma in children of average age $6\frac{1}{2}$ years. 9 of the cases were between 3 and 6 years old. 10 of the 13 children were boys corresponding with Cushing's experience that these tumours were three times more frequent in males than in females.

Relevant to the ages at which medulloblastomas are discovered is the rate at which they grow. They are usually regarded as rapidly growing tumours with a symptomatic duration of only a few months. But as Cox noted cases of long duration are encountered. In one of our necropsy cases with a large fairly well defined but microscopically characteristic tumour of the roof of the fourth ventricle in a boy of 11 years there had been signs of internal hydrocephalus for more than 5 years.

(b) Structure and growth

The tumours are highly cellular composed of small cells of rather uniform size and shape rounded or pyriform or elongated arranged usually diffusely but occasionally in rosettes, clumps or drifts (Figs 401-403). Special stains are usually

- granular layer of the foetal cerebellar cortex. It is of course easy to deduce too much from mere resemblance, but the suggestion that the cerebellar medullo blastomas represent immature cerebellar cortical tissue is supported also by their usual situation and their age incidence. If this view is correct, the cells are immature cerebellar neuroblasts and spongioblasts. Their failure to display conspicuous nerve cell differentiation would not be surprising, for the small cells of even fully differentiated cerebellar cortex do not possess highly distinctive characters permitting their ready identification. In an embryonic tumour it might well be impossible to distinguish immature neuroblasts of this kind from immature spongioblasts.

(5) Neuro-epithelioma or medullo epithelioma

'Medullo epithelioma' was the name introduced by Bailey and Cushing to denote tumours containing spaces lined by layers of primitive neuro epithelium resembling that of the embryonic medullary plate. "Neuro epithelioma" has been applied to tumours of prominently rosetted structure. While it is quite probable that truly embryonic neuro epithelial tumours exist there is no doubt that these names have been improperly applied to several different kinds of growths, some of which are not embryonic. The fallacies and difficulties of this subject are as follow

- (a) Adult ependymomas have been mis identified as 'neuro epitheliomas'. As Russell (1939) pointed out, this applies to Bailey and Cushing's original report as well as to many later reports. Adult ependyma has cilia and adult ependymomas may contain cavities surrounded by rosettes of ciliated cells. The 'neuro epithelioma' in a man of 65 reported by McLean and Lantieri is a good example of misapplication of the name to a well differentiated ependymoma. Probably most supposed 'neuro epitheliomas' in adults are ependymomas.
- (b) Even choroid plexus tumours have been mistaken for embryonic tumours. Thus Greenfield described as a primary "medullo epithelioma" of the cauda equina in a man of 48 years a tumour which was accompanied by a papillary growth in the fourth ventricle and by deposits of similar growth in the cisterna magna and theca, and the figure shows plainly a papillary tumour of the choroid plexus.
- (c) A teratoma with abundant neural tissue could easily be mistaken for a 'neuro epithelioma'. Distinction between the two could only be made with certainty by thorough microscopical study of all parts of the growth and this has seldom or never been carried out on reported cases. Consequently while it is possible that the tumours containing undoubted embryonic neuro epithelial tissue described by Bucy and Muncie, Greenfield (first case) Bailey *et al* (1939 Fig 85) and by Hirsch and Oldberg were indeed pure embryonic neuro epithelial growths, this remains uncertain. Of the 4 tumours just cited, 3 were from the neighbourhood of the fourth

transitions to astrocytic cells can sometimes be traced. This applied to one of Cox's tumours and to two others which I have examined. In making this interpretation, it is of course important not to be misled by residual included astrocytes of the invaded tissues. The evidence for the differentiation of nerve cells within the tumours remains inconclusive. The growths display a remarkable proclivity for diffuse invasion of the leptomeninges and also of the nervous tissues (*see below*).

(c) *Histogenesis*

The precise origin of medulloblastomas is still uncertain, but from their cytology and age incidence there is little room for doubt that they are truly embryonic tumours arising from still immature neural tissues during foetal life

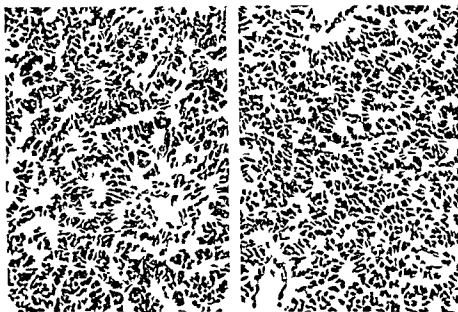


FIG. 403.—Peculiar cellular gloma of cerebrum of a girl aged 14 composed of small angular undifferentiated cells arranged uniformly in small clumps and rosettes provisionally classified as medulloblastoma ($\times 150$)

or early childhood. In this respect they are comparable with the neuroblastomas of the sympathetic system and the retinoblastomas though of course it is a mistake to confuse these three distinct kinds of embryonic neural tumours as some writers have done.

Bailey and Cushing introduced the name medulloblastoma to suggest that the growths consisted of immature bipotential cells akin to Schaper's indifferent cells of the developing brain. Embryologists have observed that proliferating undifferentiated cells persist in various parts of the growing brain long after birth and that this postnatal proliferation is much more active in certain regions especially that of the rhombic lip from which formation of the cerebellar cortex proceeds and which is the favourite region of origin of medulloblastomas. Tuthill found many immature cells in various parts of infants' brains as late as 2 years after birth.

I have been struck with the close resemblance commented on also by Stevenson and Echlin between the structure of medulloblastomas and that of the

only in experienced hands, that even then mistakes can be made, and that all rapid diagnoses should be checked from properly prepared sections of fixed tissues

THE METASTASIS OF GLIOMAS

(1) Metastasis in the cerebrospinal spaces

This has already been referred to in Chapter 10. The frequent dissemination of medulloblastomas in the cranial and spinal meninges is now well known (Cairns and Russell, Wanke, and Fig 402). Thecal dissemination from astrocytic gliomas has been recorded by Cairns and Russell, Russell and Cairns, and Eden. Intra-ventricular metastasis from oligodendroglioma was observed by Martin.

(2) Remote metastasis

Metastasis by the blood stream probably never takes place from gliomas. I know of only three reported cases in which this is supposed to have occurred. Davis (1928) saw a case which he regarded as a "spongioblastoma" of the brain with metastases in the left lung and in the soft tissues of the thoracic wall and arm, but the account is brief and incomplete, the illustrations are compatible with anaplastic carcinoma, and there is little doubt that a primary growth in the lung or some other part was overlooked. So also the tumour reported by Mittelbach (1934 and 1935) as a "glioblastoma" with metastases in the lungs was probably a primary bronchial carcinoma with a large cerebral metastasis. In a man of 28 years with a cerebellar tumour diagnosed as an 'atypical medulloblastoma' (or possibly "sarcoma"), Nelson saw several discrete metastatic nodules in the vertebrae, all the viscera are said to have been clear, but the figures are not incompatible with anaplastic carcinoma.

GLIOMAS IN ANIMALS

Gliomas in animals are probably not as rare as the paucity of reports would suggest. Jungherr and Wolf reviewed a number of recorded cases in the dog, cat, ox, horse, fowl and other birds, and they gave a good account of two astrocytomas in fowls. Belmonte also clearly described an astrocytoma in a fowl. Schlotthauer and Kernohan described an astrocytic glioma in a dog, and a tumour resembling human medulloblastoma was found in a 3 year old dog by Neubuerger and Davis. Gliomas appear to be excessively rare in rodents, the only possible instance I have been able to discover is the cellular endothelioma of the cerebrum found by Slye *et al* during their examination of over 11,000 brains of mice.

PINEALOMAS

Several kinds of tumours arise in the pineal gland—teratomas, pinealomas, and occasionally true gliomas. The pinealomas, though not gliomas, are conveniently considered here. The pineal teratomas are discussed in Chapter 61.

ventricle in young children and the other was from the pituitary region of a youth of 19

SOME SPECIAL FEATURES REGARDING THE STRUCTURE OF GLIOMAS

(1) Tissue culture of gliomas

Tissue culture has proved to be a valuable adjunct in studying the cytology of gliomas. Buckley (1929) cultured multiform glioblastomas and found a close correspondence between the cellular characters in cultures and in sections of the growths including pleomorphism, multinucleation and the formation of astrocyte-like cells. Russell and Bland (1933 and 1934) confirmed this, and also found that the migrating cells in cultures of medulloblastoma, oligodendroglioma and astrocytoma retained their specific characters. In cultures of multiform spongioblastomas, cells resembling astrocytes were often produced, strongly supporting the view that these growths are anaplastic astrocytic tumours. Bailey's "unipolar spongioblastoma" was proved by culture to be an astrocytoma. A cinematographic record of this work was made (Canti, Bland and Russell). Cox and Cranage also observed the migration of typical astrocytes from explants of astrocytoma in culture, and the migration of pleomorphic tumour cells from explants of glioblastomas.

(2) Calcification in gliomas

Almost any of the slowly growing kinds of intracranial tumours may calcify sometimes sufficiently to be visible in skiagrams. This applies to meningiomas, pituitary and parapituitary tumours, pineal tumours, tumours of the choroid plexus, haemangiomas and gliomas. The gliomas most prone to calcification are the oligodendrogliomas and the more chronic of the astrocytomas. The calcification sometimes appears first in the form of scattered spherules or irregularly in degenerated areas, but much more frequently it commences in the walls of blood vessels which finally become converted into completely calcified tubes as depicted by Bailey and Bucy and by Martin in oligodendrogliomas. This vascular or perivascular calcification sometimes involves also the vessels in the brain tissue peripheral to the tumour.

(3) Intranuclear inclusion bodies in gliomas

In astrocytic gliomas, especially anaplastic ones, Russell (1932) frequently observed conspicuous intranuclear bodies resembling those often described as characteristic of virus infections. This observation should be taken not to suggest a virus causation for gliomas, but as a warning to virologists and others not to be misled by odd structural changes in tumour cells.

(4) Rapid diagnosis of gliomas by wet film smears and squashes

As Russell *et al* (1937) have shown, rapidly stained smears or squashes of fragments of tissue are capable of giving useful information as to the presence and nature of a tumour for the guidance of the surgeon during the operation. I can confirm this from my own experience with a rapid haematoxylin-eosin method. But I think it important to emphasize that such methods are useful

due neither to destruction of the pineal gland nor to endocrine secretions of the pineal tumour cells, for precocity occurs with teratomas devoid of pineal elements (as in Horrax and Bailey's sixth case) and is in fact commoner with teratomas than with pinealomas (Bochner and Scarff), and it may occur also with non pineal tumours of neighbouring parts (Le Marquand and Russell). It seems probable, then, that the precocity which may accompany pineal tumours is due to functional disturbance of neighbouring structures, especially the hypothalamus, or possibly to some constitutional peculiarity of the patients which also underlies the development of the tumours.

(4) Pinealomas in animals

The only record I know of is that of Schlotthauer and Kernohan, who saw a large pinealoma in a silver fox.

REFERENCES

- ALPERS, B. J., and ROWE S. N. (1937) The astrocytomas, *Amer J Cancer*, 30 1
(A useful well illustrated account.)
Bailey O. T. (1936) *Arch Path* 21 584
Bailey P. (1932) Penfield's *Cytology and Cellular Pathology of the Nervous System* Vol III, p 905 New York
Bailey P., Buchanan D. N. and Bucy P. C. (1939) *Intracranial Tumors of Infancy and Childhood* Chicago
BAILEY, P. and BUCY, P. C. (1929) Oligodendrogliomas of the brain *J Path Bact*, 32 735 (The best account of the subject beautifully illustrated.)
BAILEY, P. and CUSHING, H. (1926) *A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis* Philadelphia
Belmonte V. (1935) *Virchows Arch* 294 329
Bergstrand H. (1937) *Virchows Arch* 299 725
Bochner S. J. and Scarff J. E. (1938) *Arch Surg* 36 303
Bratton A. B. and Robinson S. H. G. (1946) *J Path Bact* 58 643
Buckley R. C. (1929) *Amer J Path* 5 467
BUCY, P. C., and GUSTAFSON, W. A. (1939) Structure, nature and classification of the cerebellar astrocytomas *Amer J Cancer* 35 327
Bucy P. C. and Muncie W. S. (1939) *Amer J Path* 5 157
CAIRNS, H. and RUSSELL, D. S. (1931) Intracranial and spinal metastases in gliomas of the brain *Brain* 54 377
Canti R. G., Bland J. O. W. and Russell D. S. (1935) *Proc Assoc Res in Nervous and Mental Disease* 16 1
COOPER E. R. A. (1935) The relation of oligocytes and astrocytes in cerebral tumours *J Path Bact* 41 259
COURVILLE C. B. (1936) Multiple primary tumors of the brain *Amer J Cancer* 26, 703
COX, L. B. (1933) The cytology of the glioma group, with special reference to the inclusion of cells derived from the invaded tissue *Amer J Path* 9 839
Cox L. B. (1937) *J Path Bact* 44 661
Cox L. B. and Cranage M. L. (1937) *Ibid* 45 477
Davis L. (1928) *Ann Surg* 87 8
Eden K. C. (1938) *Brain* 61 298
Globus J. H. (1941) *Arch Path* 31 533
Globus J. H. and Kahlenbeck H. (1942) *Ibid* 34 674
Globus J. H. and Silbert S. (1931) *Arch Neurol Psych* 25 937
Greenfield J. G. (1934) *J Path Bact* 38 11
Hirsch E. F. and Oldberg E. (1938) *Zbl allgem Path* 69 113
Horrax G. and Bailey P. (1925) *Arch Neurol Psych* 13 423
Jungherr E. and Wolf A. (1939) *Amer J Cancer* 37 493

(1) Age and sex incidence

Most pinealomas occur in children adolescents or young adults cases over 30 years of age are exceptional Four out of 7 patients described by Globus and Silbert were under the age of puberty Males are much more often affected than females

(2) Structure and histogenesis

The structure usually regarded as characteristic consists of a mosaic of ill defined groups of large rounded cells bordered by zones of small darkly staining cells The former are regarded as pineal tumour cells proper but opinions differ as to the nature of the latter Bailey and Cushing and Bailey (1932) described these as connective tissue stroma containing lymphoid cells and Globus and Silbert also regarded them as young stromal cells which become fibroblasts These workers likened the pattern discernible clearly or vaguely in many pineal tumours to the distinct mosaic structure of the foetal and infantile pineal gland in which also they supposed the zones of small cells bordering the units of the mosaic to be young mesenchymal cells This view, however is at variance with the opinions of most embryologists, and is moreover, refuted by Globus and Silbert's own excellent photographs of young pineal glands These show plainly that the small cells of the border zones of the foetal mosaic are not stromal but pineal parenchyma cells with all transitions to the larger central cells of the nodular areas In a genuine pinealoma then we may expect to find both large and small tumour cells with transitions between them an expectation which is realized in specimens like that depicted in Russell's figures 19 and 20 (1944) Horrax and Bailey's use of the name 'spongioblastoma' in reference to poorly differentiated tumours of the pineal gland is confusing and has properly not been adopted

As Russell has pointed out confusion regarding the structure of pinealomas has been caused by including under this title some teratomas Malignant teratomas of the pineal as well as those of the testis and other parts (see Chapter 61) often contain extensive areas of mosaic structure in which groups of large rounded embryonic cells are bordered by stroma with collections of lymphocytes These areas may superficially resemble the mosaic areas of true pinealomas and it is this confusion of the two which has led to the idea that the small cells of pinealomas are lymphoid Every pineal tumour must be very thoroughly and completely examined and until this is done on a sufficiently large series of specimens, uncertainty must remain regarding the relative frequency and properties of the two distinct kinds of pineal tumours pinealomas and teratomas Russell may well be correct in her opinion that most pinealomas which have been reported have probably been teratomas and that true pinealomas are much rarer The whole subject of pineal tumours and their structure is in need of review especially by complete examination of the tumours and careful cytological study

(3) Endocrine disturbances associated with pineal tumours

Pineal tumours either pinealomas or teratomas, occurring in young children have often been accompanied by precocious bodily mental or sexual development (Horrax and Bailey) The explanation of this is still obscure It appears to be

CHAPTER 53

PAPILLARY TUMOURS OF THE CHOROID PLEXUS

WE ARE NOT concerned here with the rather common non neoplastic cystic and degenerative enlargements of the choroid plexus, which are often present in mild degree in middle aged and elderly subjects and occasionally large enough to produce symptoms. Most of the "psammomas" of the ventricles, including the large masses found in the ventricles of horses, are of this nature. True tumours of the choroid plexus are reported as papillomas or papillary carcinomas, but attempted separation into benign and malignant growths is quite arbitrary and serves no useful purpose. One of the first clearly described cases was that of Douty (1886). The most useful recent accounts are those of Davis and Cushing, Van Wageningen, Turner and Simon, and Posey. The following personally studied case illustrates most of the features of the disease.

Case I—Male aged 57. *History*—Weakness of legs ataxia and falling to right side for 12 months. Examination disclosed nystagmus right lower facial paresis and defective sensation of right side of face. *Diagnosis* cerebello pontine angle tumour. *Operation* partial removal of large firm but friable vascular tumour from this region patient died 3 days later from broncho pneumonia. *Necropsy*—Large residual mass of growth lay in cerebello pontine angle deeply indenting dorsal part of pons but projecting only slightly into 4th ventricle. Scattered here and there on the surface of the spinal cord and spinal nerve roots there were several small white or grey nodules the largest 3 millimetres in diameter. Except for pneumonia thoracic and abdominal organs were normal. *Histology* (Figs 404-405)—Well differentiated papillomatous growth closely resembling normal choroid plexus and showing much granular calcification. The implant nodules on the spinal cord are of similar structure.

(1) Age and sex incidence

Van Wageningen noted that the incidence of these growths is greatest in the first decade and declines with increasing age. The ages of 72 cases reviewed by Posey were as follows

Decades - - -	1	2	3	4	5	6	7	8
No. of cases - - -	27	9	11	7	10	5	2	1

In one case the growth was found in a new born infant. Van Wageningen's first case was only 3 months old and Posey's case 6 months. The sexes appear to be about equally liable.

(2) Site

The fourth ventricle is the commonest site nearly 50 per cent of the growths arising here. Rather fewer tumours arise in the lateral ventricles and about 15 per cent in the third ventricle. Of 34 lateral ventricular tumours reviewed by Posey, 22 were left sided, 11 right sided and 1 bilateral. The almost completely

- Kernohan J W Woltman H W and Adson A W (1931) *Arch Neurol Psych* 25 679
- Kwan S T and Alpers B J (1931) *Arch Neurol Psych* 26 279
- LE MARQUAND H S and RUSSELL D S (1934-1935) A case of pubertas praecox (macrogenitosomia praecox) in a boy associated with a tumour in the floor of the third ventricle *Royal Berkshire Hosp Rep* p 31 (Contains a good discussion of precocity and its relationship to pineal tumours)
- Martin J P (1931) *Brain* 54 330
- MARTIN, P, and CUSHING, H (1923) Primary gliomas of the chiasm and optic nerves in their intracranial portion *Arch Ophth* 52 209 (An excellent well illustrated account of 7 cases)
- Maximow A A and Bloom W (1944) *Text book of Histology* Philadelphia
- McLean A J and Lantieri S R (1936) *Arch Path* 21 601
- Mittelbach M (1934) *Verh Dtsch path Ges* 27 70
- Mittelbach M (1935) *Beitr path Anat* 95 538
- Nelson A A (1936) *Amer J Cancer* 28 1
- Neuburger K T and Davis C L (1943) *Cancer Res* 3 243
- Nevin S (1938) *Brain* 61 170
- Penfield W (1931) *Brit Med J* 1 337
- Russell D S (1932) *J Path Bact* 35 625
- RUSSELL D S (1939) The pathology of intracranial tumours *Post grad Med J* 15 150 (An excellent outline)
- RUSSELL D S (1944) The pinealoma its relationship to teratoma *J Path Bact* 56 145 (A timely provocative paper)
- RUSSELL D S and BLAND J O W (1933) A study of gliomas by the method of tissue culture *J Path Bact* 36 273
- Russell D S and Bland J O W (1934) *Ibid* 39 375
- Russell D S and Cairns H (1930) *J Path Bact* 33 383
- Russell D S and Ellis R W B (1933) *Arch Dis Child* 8 329
- Russell D S Kräyenbuhl H and Cairns H (1937) *J Path Bact* 45 501
- SCHERER H J (1938) Structural development in gliomas *Amer J Cancer* 34 333 (An important study of gliomas by large sections in serial planes)
- SCHERER H J (1940) Cerebral astrocytomas and their derivatives *Amer J Cancer* 40 159 (An excellent account stressing the structural diversity of the group)
- Schlotthauer C F and Kernohan J W (1935) *Amer J Cancer* 24 350
- Singer L and Seiler J (1933) *Virehows Arch* 287 823
- Slye M Holmes H F and Wells H G (1931) *Amer J Cancer* 15 1387
- Stevenson L and Echlin F (1934) *Arch Neurol Psych* 31 93
- Tuthill C R (1938) *Arch Path* 26 791
- VERHOEFF F H (1922) Primary intraneural tumors (gliomas) of the optic nerve *Arch Ophth* 51 120 239 (A good account of 11 cases)
- WANKE R (1933) Zur anatomie und chirurgie des medulloblastoms *Arch klin Chir* 177 528 (A good account of the structure and spread)
- Willis R A (1934) *The Spread of Tumours in the Human Body* London

irregular tumour filling and distending the left lateral and third ventricles.

Microscopically, almost all of the growths are of fully differentiated plexus like structure, and calcified spherules like those of the normal plexus are often present, especially in adults. Turner and Simon, however, saw anaplastic features—multinucleation and many mitoses, in their two tumours, which they therefore regarded as being malignant. Needless to say, marked anaplasia in a supposed choroid plexus tumour demands consideration of the possibility of it being a metastasis of an unsuspected glandular carcinoma elsewhere in the body, especially in the lungs, a possibility which only post mortem examination can eliminate.

(4) Metastasis

Because of the benign micro structure and non-invasive character of the growths, some writers have preferred to speak of 'seeding' rather than metastasis 'via the cerebrospinal fluid'. This seems to me to be a distinction without a difference, for what is metastasis but successful transplantation of tumour fragments?

The following are good examples of the dissemination of plexus tumours by the cerebrospinal fluid. Bielschowsky and Unger saw a papillary growth of the lateral recess of the fourth ventricle with multiple small implants on the basal meninges and cerebral cortex. From a tumour of the posterior horn of the lateral ventricle Kono saw implants in the subarachnoid spaces and on the cranial nerves. The papillary tumour of the fourth ventricle described by Toppisch had disseminated widely in the cranial and spinal meninges. Intraventricular implants were recorded by Van Wagenen (second case) and by Cairns and Russell. Schuster saw diffuse and nodular thickening of the cranial meninges, which was mistaken at first for tuberculous meningitis but which proved to be glandular carcinoma; this may have arisen in the plexus of the third ventricle, but the possibility of metastasis from an undetected primary carcinoma elsewhere cannot be quite excluded. (See also Case I above and Fig. 405.)

(5) Choroid plexus tumours in animals

The common 'cholesteatomas' of the choroid plexus of old horses, a large bilateral specimen of which is depicted by Nieberle and Cohrs in their Fig. 338, are not tumours but degenerative lesions. However papillary tumours comparable with the human ones do occur in animals, e.g. the 'papillary adenoma of the ependyma' of the lateral ventricle of a mouse reported by Slye *et al*.

REFERENCES

- Bielschowsky M. and Unger E. (1906) *Arch. klin. Chir.* 81 61.
 Cairns H. and Russell D. (1931) *Brain* 54 377.
 Davis L. E., and Cushing H. (1925) *Arch. Neurol. Psych.* 13 681.
 Douth J. H. (1886) *Brain* 8 409.
 Kono N. (1924) *Frankfurt Z. Path.* 30 92.
 Nieberle K. and Cohrs P. (1931) *Lehrbuch der Spez. Path. Anat. der Haustiere* p. 471. Jena.
 Posey L. C. (1942) *Arch. Path.* 34 911.
 Schuster H. (1931) *Virchows Arch.* 280 194.
 Slye M., Holmes H. F. and Wells H. G. (1931) *Amer. J. Cancer* 15 1387.

extra ventricular position of the tumour in my case showed that it arose in the fringe of plexus which projects through Luschka's foramen



FIG 404—Case I Primary papillary growth of choroid plexus ($\times 75$)

(3) Structure

The tumours are usually vascular friable visibly papillary and sometimes gritty from granular calcification. The extremes of size were exemplified by Van



FIG 405—Case I Metastasis on surface of spinal cord with calcified spherules ($\times 75$)

Wagenen's two specimens—in one case a small well circumscribed tumour which was removed successfully from the lateral ventricle and in the other a huge

CHAPTER 54

NEURILEMMOMA AND OTHER TUMOURS OF NERVE-SHEATHS

THE PRINCIPAL subject of this Chapter is the specific Schwann cell tumour or neurilemmoma, but along with this we must consider also the less distinctive fibromas of nerves, for the two kinds of growth may occur together, and there is still uncertainty regarding the histogenesis of the several components of the nerve sheaths. Closer studies of their tumours will undoubtedly help to resolve this uncertainty.

NEURILEMMOMA OR SCHWANN CELL TUMOUR

Masson's and Stout's names "Schwannoma" and "neurilemmoma", and Mallory's and Penfield's name "perineurial fibroblastoma", express the two opposing views regarding the histogenesis of this distinctive nerve-sheath tumour. As the above heading indicates, I adhere to the former view, the structural evidence appears to me conclusive that this tumour indeed consists of neurilemmal cells. The frequently used name "neurinoma", introduced by Verocay, literally means "nerve fibre tumour", and is therefore clearly inappropriate. The only really characteristic structural feature of neurilemmoma is the regimentation of its cells, the staining properties of its fibres are less distinctive.

(1) Age and sex incidence

(a) Age

The ages of Stout's 50 patients with neurilemmomas of peripheral nerves ranged from infancy to 65 years, with no preponderance at any particular age period. Nielsen's 130 patients with acoustic nerve tumours ranged from 18 to 68 years of age on admission, the highest number being in the fourth decade and the average age being 42 (in Cushing's series it was 40) but the duration of symptoms before admission is not stated. I have examined 22 surgically removed acoustic tumours: the ages of the patients at the time of operation ranged from 17 to 65; 13 of them were in the third and fourth decades, and the mean age was 37. The mean duration of symptoms was 32 months, the longest being 8 years in a man aged 51. The youngest patient, a girl aged 17, had had symptoms for one year. Following are the details of my 2 youngest cases of neurilemmoma of extra-cranial nerves.

Case I—A tumour which had been present for several years was removed from the middle of the tongue of a boy aged 15. It was a smooth encapsulated ovoid mass 1.5 centimetres in main diameter. *Histology*—Typical neurilemmoma with all cells forming regular regimented groups and the fibres taking the usual stains for collagen (Fig. 406).

Case II—Routine skiagrams of the chest of a boy aged 17 about to enter the Navy showed the shadow of a rounded mass in the upper posterior mediastinum behind the root of one lung. This was removed successfully by Mr. C. J. O. Brown of Melbourne. It was an encapsulated mass 3 centimetres in diameter composed partly of white tissue

- Toppisch G (1926) *Frankfurt Z Path* 33 238
Turner O A and Simon M A (1937) *Amer J Cancer* 30 289
VAN WAGENEN, W P (1930) Papillomas of the choroid plexus *Arch Surg* 20 199
(A valuable review including details and figs of previously reported cases)

frequency of these tumours in the wall of the stomach is noteworthy. In this situation, confusion with myomas with regimented nuclei is easy, and indeed



FIG. 407—Neurilemmoma of parotid gland: an encapsulated spherical tumour 1 centimetre in diameter from a young woman (Microscopically this was at first mistaken for a salivary adenoma of unusual type) ($\times 150$)



FIG. 408—Neurilemmoma of medulla of adrenal gland: a solitary lobulated tumour 8 millimetres in diameter found at necropsy on a man aged 51 ($\times 120$)

I doubt if distinction is always possible (see Golden and Stout). Peptic ulceration may accompany the growth, as in a case reported by Fuller,

and partly of spongy vascular spaces. *Histology*—Typical neurilemmoma with prominent regimentation of cells mixed with areas of cavernous vascular structure like that of an angioma.

(b) *Sex*

Females appear to be more liable than males, e.g. 61 and 39 per cent respectively in Nielsen's series of acoustic tumours, and 64 and 36 per cent in Cushing's series. My 22 specimens of acoustic tumour came from 15 women and 7 men. Stout's 50 patients with peripheral tumours comprised 28 females and 22 males.

(2) *Site*

(a) *Intracranial nerves*

The acoustic nerve is the commonest single site and most of the tumours arise in or near the internal meatus. In routine sections of temporal bones Hardy



FIG. 406—Case I. Neurilemmoma of tongue ($\times 150$)

and Crowe discovered several examples of tiny symptomless tumours of the auditory nerve deep in the canal. Other cranial nerves are rarely the site of neurilemmomas. Kovács saw a solitary tumour of this kind on the oculomotor nerve. Krayenbuhl reviewed the primary tumours of the trigeminal nerve and Gasserian ganglion: no doubt some of these are neurilemmomas similar to the auditory nerve tumours.

(b) *Peripheral nerves*

Stout's review of peripheral neurilemmomas showed these to occur most frequently on main nerves on the flexor aspects of the limbs in the hands, neck, scalp, face, tongue and stomach; the trunk was an infrequent site and no tumours were seen in the feet, urogenital organs, lungs, oesophagus or rectum. The

frequency of these tumours in the wall of the stomach is noteworthy. In this situation, confusion with myomas with regimented nuclei is easy, and indeed

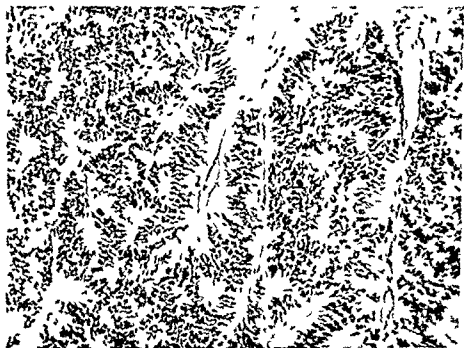


FIG 407 —Neurilemmoma of parotid gland: an encapsulated spherical tumour 1 centimetre in diameter from a young woman (Microscopically this was at first mistaken for a salivary adenoma of unusual type) ($\times 150$)

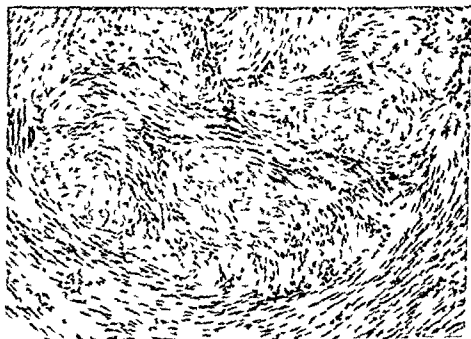


FIG 408 —Neurilemmoma of medulla of adrenal gland: a solitary lobulated tumour 8 millimetres in diameter found at necropsy on a man aged 51 ($\times 120$)

I doubt if distinction is always possible (see Golden and Stout). Peptic ulceration may accompany the growth, as in a case reported by Fuller,

and in a similar specimen which I examined. Other sites of neurilemmomas in my series included the tongue (Case I), parotid gland (Fig 407) the posterior



FIG 409—From the same specimen as Fig 408 showing two nerve cells included within the whorled regimented tumour tissue ($\times 350$)

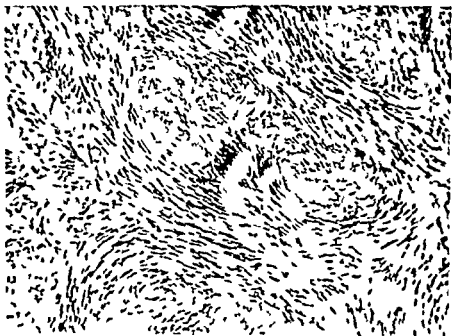


FIG 410—Subcutaneous neurilemmoma of the back of a woman aged 45 ($\times 120$)

mediastinum (Case II) the scalp (Case III below) the intestine (Case VII below) the medulla of the adrenal gland (Figs 408 409) the subcutaneous tissue of the back (Figs 410 411) and the spinal theca (Fig 412)

(3) Number of tumours, and concomitant lesions

In most cases, structurally typical neurilemmomas are solitary growths unaccompanied by signs of neurofibromatosis or other lesions of the nervous system. In a minority of cases however, the tumours are multiple or are accompanied by neurofibromatosis or by minor stigmata of that disease. This applied to 9 of Stout's 50 cases. Generalized neurofibromatosis may include bilateral acoustic tumours, as in Gray's cases, and bilateral acoustic tumours are sometimes the principal manifestation of familial neurofibromatosis (Gardner and Turner). My personally studied cases of neurilemmoma included one

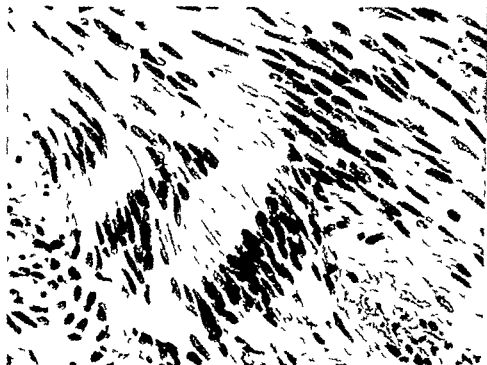


FIG 411—Detail of Fig 410 ($\times 400$)

showing 3 separate tumours in the wall of the small intestine in a woman aged 58 another of multiple intestinal tumours in a woman aged 47 with neurofibromatosis (Case VII below) and the following case with 2 tumours

Case III—For years a woman aged 45 had noticed 2 small rounded subcutaneous tumours one of the neck and one of the scalp. These were diagnosed sebaceous cysts and were excised. They proved to be solid tumours microscopically typically regumated neurilemmomas.

The presence of a neurilemmoma therefore calls for careful search for tumours of nerves in other parts of the body, but in most cases none will be found.

(4) Structure

(a) Naked eye appearance

A neurilemmoma is well circumscribed and often encapsulated, and, if it arises from a large nerve, it shows the intact nerve bundles passing to one side of it or spread out over its surface. Most tumours are rounded or ovoid but

and in a similar specimen which I examined. Other sites of neurilemmomas in my series included the tongue (Case I) parotid gland (Fig 407), the posterior



FIG 409—From the same specimen as Fig 408 showing two nerve cells included within the whorled regimented tumour tissue ($\times 350$)

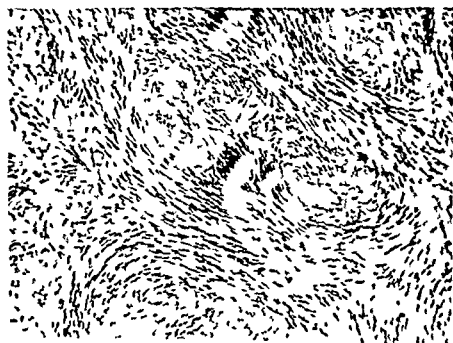


FIG 410—Subcutaneous neurilemmoma of the back of a woman aged 45 ($\times 120$)

mediastinum (Case II) the scalp (Case III below) the intestine (Case VII below), the medulla of the adrenal gland (Figs 408 409) the subcutaneous tissue of the back (Figs 410 411) and the spinal theca (Fig 412)

in which regimentation is scanty or indefinite are indistinguishable from ordinary fibromas

(ii) *Reticular* or so-called "type B" tissue shows a disorderly loose meshwork of cells of variable shapes, often with plentiful intercellular vacuoles or microcysts containing watery or mucinoid fluid which stains bluish with haematoxylin. Regimented cells and parallel fibre-bundles are not found, and indeed collagen fibres are scanty or absent. Type A and type B tissues are often present together, they are continuous with one another, but their junctions are usually abrupt.

(iii) A third type of structure, the *epithelioid*, is less frequently described. It shows closely aggregated plump cells with scanty intercellular spaces and fibres or with none. Over small areas this superficially resembles an epithelial structure, but elsewhere it passes into the fasciculated or reticular type of growth. I have seen this rather misleading type of structure in only two tumours, both from the stomach.

Nerve fibres are rarely to be found in the substance of the tumour, they lie outside the capsule, or at the most a few residual fibres may be found just within its margins.

Gross degenerative changes are unusual, but collections of lipid laden foam cells are sometimes present, especially in acoustic nerve tumours.

(5) Growth and behaviour

Neurilemmomas grow slowly, remain well circumscribed and are readily cured by local removal. When the tumour involves a large nerve, it is usually unnecessary to excise the nerve, careful stripping of the nerve bundles from the surface of the growth will usually permit its enucleation. A tumour which cannot be enucleated because it involves a nerve diffusely and without encapsulation is not a neurilemmoma. Recurrence of a neurilemmoma may of course take place in situations where complete removal is not practicable as in the cerebello-pontine angle, but in easily accessible peripheral sites, enucleation has rarely been followed by recurrence. Malignant properties, infiltration and metastasis, are said never to occur (Stout), but in my opinion an open mind is still called for on this point. Is it not possible, even probable that malignant properties might be accompanied by loss of nuclear regimentation and other structural features on which the recognition of a neurilemmoma depends? In the following case an invasive malignant growth, diagnosed microscopically "neurogenic sarcoma", showed distinct regimentation in parts. Is it a neurogenic fibrosarcoma which happens to show regimentation or an invasive neurilemmoma, or a combination of both?

Case IV—For 2 years a woman aged 47 had noticed an increasing mass in the subcutaneous tissue of the abdominal wall below the navel. Recently this had grown more rapidly and some small satellite growths had developed around it. It was excised along with the overlying skin. The main mass was rounded, 3 centimetres in diameter, well defined but was connected by strand like outrunners with 4 smaller adjacent nodules all composed of firm white fasciculated tissue. Though not adherent to these growths the skin overlying them showed irregular white thickening of the dermis over an area 3 centimetres in diameter. *Histology*—Moderately cellular whorled and fasciculated spindle-celled growth well circumscribed in some places but diffusely infiltrating the subcutaneous tissue and dermis in others. Prominent regimentation of the cells is

the tumour depicted in Figs 410 and 411 was an elongated tortuous cylindrical growth 6.5 centimetres long and 1.8 centimetres in diameter. The tumour tissue is usually of uniform texture, soft or moderately firm in consistency, and pink, grey or yellowish in colour. Large tumours sometimes show some hydropic or cystic change.

(b) *The microscopic structure*

The following rather distinct but of course not sharply separable patterns are encountered.

(i) *Fasciculated* or so called 'type A' tissue is the most characteristic, often enabling the tumour to be identified at a glance. It shows an orderly arrangement

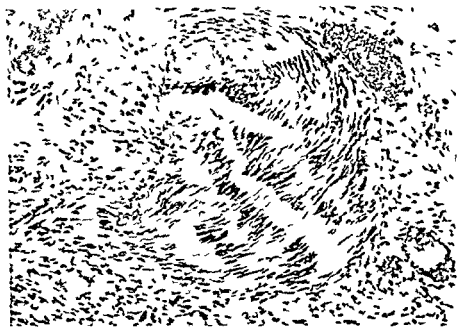


FIG. 412.—Intrathecal neurilemmoma from a woman aged 55 ($\times 120$)

of parallel cells and intercellular fibres, forming interwoven bundles. In these the cells often lie in transverse parallel ranks separated by nucleus free zones of densely aggregated fibres along with the terminal portions of the cells. This alternation of fibrous and nuclear zones gives the distinctive palisaded or regimented pattern. The regimentation may be in simple parallel bands or may take sinuous or complicated forms. Masson drew attention to the close resemblance of the structure of palisaded tumour nodules to that of the neurilemmal supporting elements of Wagner-Meissner tactile corpuscles and supported this comparison with some convincing photographs. Distinct regimentation is not always present or it may be so scanty that it must be sought for. The neurilemmoma fibres consist of a form of reticulin or collagen which however stains somewhat differently from fibroblastic collagen. With Van Gieson's stain it often assumes varying tints of yellow, orange and brown but in old dense tumours it stains red or pink like mesenchymal collagen. Old collagenous neurilemmomas

unchanged Does it not indicate that what we class under the general term of connective tissue is not uniform either in structure or function, but in each organ or system may have its own special endowment ? ”

(1) Personally studied cases

The following personally studied cases of neurofibromatosis exemplify many of the features of the disease

Case V—Male aged 40 A pale wizened bent man appearing much older than his age had 10 brothers and sisters all healthy and there was no record of similar disease



FIG 414—*Case V* Neurofibromatous thickening of dermis including a nerve with great thickening of its sheath ($\times 18$)

in any other near relatives The patient had hundreds of small painless skin tumours on his trunk limbs and neck with patchy pigmentation of the skin These had been present since childhood and had grown only slightly The largest growth in one thigh had increased in size from a diameter of 5 centimetres when he was 28 years old to 6.5 centimetres 12 years later This tumour and a smaller adjacent one were excised microscopically they were soft semi-translucent fairly well defined masses typical benign neurofibromata of only moderate cellularity with no regimentation and with recognizable nerve fibres traversing the whorled fibroblastic tissue in places (Fig 414)

Case VI—Male aged 35 with no family history of neurofibromatosis had had a swelling in the right side of the neck since childhood without any increase in size in recent years Recently he had noticed atrophy of right thenar bilateral deafness and some headaches Examination showed a large diffuse firm swelling in the right upper neck with small extensions in the lower part of the neck an ill defined nodular mass 3 centimetres in diameter in the right axilla a well defined subcutaneous mass 2 centimetres in diameter on the outer aspect of left thigh a small projecting nodule on the back of the scalp many pigmented patches on the skin of the trunk slight bilateral proptosis of

- * present in parts especially where the growth infiltrates adipose tissue (Fig 413) The intercellular matrix is partly collagenous and fibrous and partly mucinous Mitotic figures are few even in poorly differentiated cellular areas

NEUROFIBROMATOSIS

I do not propose to give a detailed account of the protean manifestations of this disease From an enormous literature I suggest the following papers for useful descriptions, reviews and sources of reference on visceral neurofibromatosis Banarjee and Christeller Grill and Kuzma, Barton and Inglis, Meyer,

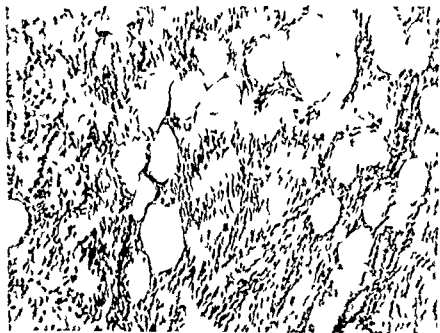


FIG 413—Case II Malignant neurilemmoma of abdominal wall showing regimented cells infiltrating subcutaneous adipose tissue ($\times 120$)

on the association of neurofibromatosis with tumours or other lesions of the brain, spinal cord and meninges Harbitz Martz Scharrer Scherer Worster Drought *et al* Turner and Gardner or with tumours of the optic nerve or its sheaths Davis on the hereditary character of neurofibromatosis Gardner and Turner Turner and Gardner Grill and Kuzma on histogenesis Scherer Turner and Gardner, Bailey and Herrmann and on sarcomatous change Stewart and Copeland (*see also below*) Neurofibromatosis may also be associated with pigmented moles (Chapter 58) with lipomas (Chapter 42) with chromaffin tumours (Rosenthal and Willis) with rhabdomyosarcomas (Masson and Martin) or with cranio facial or other malformations (Weber and Bode Grill and Kuzma and other references by Stewart and Copeland) Muller described congenital neurofibromatous macroglossia Good descriptions of plexiform neurofibromatosis include those of De Morgan and Coupland and Plenge The following comment of the former made in 1875 is worth citing 'It is an interesting pathological fact that we may have a disposition to new growths pervading extensively the connective tissue of nerve alone while all other parts of the body remain

or involves nerves diffusely for variable distances. Nerve fibres are often to be found traversing the tumours. Whorls and fasciculi in the growth often clearly follow patterns determined by the inclusion of neurofibromatous nerve bundles within it. It is as if the entire nerve has suffered expansion, with separation of all its constituent fibres by a universal diffuse increase of all its sheath tissues. The general structure and staining properties of the bulk of the tissue are usually similar to those of mesenchymal fibrous or mucoid tissue, but in some tumours or parts of tumours the staining properties of the fibres are indefinite and not characteristic of collagen. Definite Schwann cells of the affected nerves can often be recognized in the growths, but it is often impossible to identify individual cells as either Schwannian or fibroblastic. Many workers have concluded that the bulk of the neurofibromatous tissues is endoneurial or perineurial and fibroblastic (e.g. Bailey and Herrmann), others that it is mainly Schwannian (e.g. Stewart and Copeland).

That Schwann cells do participate in the tumours in generalized neurofibromatosis is shown by cases like Nos VI and VII above, in which characteristic regimentation was found in one or more tumours. Reference has already been made also to Stout's finding that some cases of neurilemmoma show minor signs of neurofibromatosis, and to the occurrence of acoustic neurilemmomas in cases of generalized neurofibromatosis.

(3) Sarcomatous change in neurofibromatosis

The proneness of the lesions of neurofibromatosis to sarcomatous change has long been recognized. One of the earliest reports was that of Coupland and Balding (1877) who, in a patient with multiple subcutaneous fibromas, saw a myxosarcoma of the sciatic nerve with pleural and mediastinal metastases. Other noteworthy reports and reviews include those of Westphalen, de Santi, Hartman, Quick and Cutler, Plenge, Lewis and Hart, Hosoi, and Stewart and Copeland (See also Case VII above).

The structure of the malignant growths is very variable. Many contain myxosarcoma like areas, some resemble fibrosarcomas and others are highly cellular spindle celled or pleomorphic-celled growths. Large compact masses or smaller groups of plump polyhedral cells are not uncommon, giving parts of the tumours a resemblance to anaplastic carcinoma. Of course, these characters afford little or no reliable evidence regarding the histogenesis of the neurofibromas but, as a group neurogenic sarcomas are rather different from the ordinary sarcomas of non neural mesenchymal tissues.

(4) General comments on neurofibromatosis

(i) In spite of the great diversity of its clinical appearances, neurofibromatosis is one disease. Multiple, cutaneous or visceral growths, diffuse plexiform growths, neurofibromatous elephantiasis of limbs or other parts, are all manifestations of a similar change.

(ii) Most of the benign lesions of neurofibromatosis are not true tumours but tumour like developmental anomalies or hamartomas. In many cases the growths remain stationary or increase in size only slowly over a period of many

the eyes and marked deafness. The thigh tumour was excised; microscopically it showed whorled areas, spindle-celled areas with regimented cells, much loose poorly cellular connective tissue and some cystic spaces.

Case VII—Female, aged 47. Since childhood skin of trunk and limbs had been covered with hundreds of small sessile tumours. For last few months she had suffered from pain in left thigh, weakness and an increasing abdominal mass. **Necropsy**—Retroperitoneal tumour 33 centimetres in diameter extended from lower pole of left kidney to pelvis, adherent to vertebrae and to intestine; on section tough, fibrous, with degenerated areas and cysts. Multiple well-defined white fasciculated tumours were



FIG. 415—*Case VII*. Neurofibroma of small intestine with included nerve cells of Auerbach's plexus. ($\times 80$)

present in wall of small intestine, the largest 4 centimetres in diameter; other viscera unaffected. **Histology**—Large tumour, spindle-cell fibrosarcoma. Small tumours, whorled and fasciculated, benign spindle-celled growths, with slight regimentation in parts, and with included cells of Auerbach's plexus (Fig. 415).

Case VIII (Reported by Rosenthal and Willis)—Male, aged 52. **Necropsy**—Many small cutaneous neurofibromata, devoid of regimentation; bilateral chromaffin-cell tumours of the adrenals; fatal pulmonary tuberculosis.

These cases severally illustrate the not unusual absence of a family history of the disease; the frequently long duration of the tumours with little or no increase in size; the sporadic distribution of tumours in some cases; multiple intestinal tumours; associated chromaffin tumours; the usual absence of microscopical evidence of the presence of Schwann cells; but on the other hand the occasional presence of regimentation (Cases VI and VII) and the supervention of sarcoma.

(2) Structure of neurofibromata

In most cases the structure of the multiple growths of neurofibromatosis is unlike that of the solitary neurilemmoma. The tumour tissue is not well-circumscribed or encapsulated but mingles with the surrounding dermal or other tissues.

regimented growths with fibres staining quite unlike collagen and densely collagenous growths resembling ordinary fibromas. This demonstrable collagen forming property of Schwann cells at once impels attention to the possibility, suggested by Masson, that the supposedly fibroblastic endoneurium and perineurium may be of neurolemmal origin or at least may contain neurolemmal elements. Or, granting that the components of nerve sheaths may come from two distinct sources, perhaps they form a unified system, in which germ layer distinctions have little meaning and in which there is a gradation of cell properties, from those of the distinctive Schwann cells in immediate contact with the nerve fibre to those of the non distinctive fibroblasts of the epineurium and perineurium remote from the nerve fibre.

In taking this view we would abandon sharp distinction between the supposedly ectodermal and mesenchymal constituents of nerve-sheaths and would regard the properties of particular cells as determined by their positions in the nerves and not by their germ layer origin. Adoption of this view would largely resolve the difficulties in interpreting the structure of nerve sheath tumours. According to it, we might expect to encounter tumours of distinctive Schwann cell type, others of non distinctive mesenchymal type, and others of associated, combined or transitional type. And this, in fact, is what we find.

NEURO EPITHELIAL TUMOURS OF NERVES

None of the few reports of supposedly primary epithelial tumours of nerves is acceptable. Stout (1918) described a patient with large tumours in the axilla and in the course of the ulnar nerve, composed of masses of epithelium like tissue containing rosettes said to resemble those of retinoblastoma. In the absence of follow up and necropsy findings, it is impossible to exclude the possibility of a primary carcinoma of the lungs or of some other organ in this case. Cohn reported the case of a man with a carcinomatous tumour of the cubital fossa involving the radial nerve, and although necropsy disclosed a large carcinoma of the right lung and metastases in many other organs, Cohn inclined to the clearly erroneous view that the cubital tumour was a primary epithelial growth of the radial nerve. Under the title 'malignant neurinoma with epithelial elements', Brandes described a large tumour of the thigh in an old man; this was spindle celled but contained epithelial clumps, and epithelial metastases were found in lymph glands and lungs. Brandes stated that no other primary growth was found, but failed to mention the stomach, pancreas, thyroid and several other epithelial organs. Stout (1935) reviewed the reported cases of supposedly primary epithelial tumours of nerves and accepted 3 of them, but noted that they all differed in structure. Stout and Murray reported as 'neuro epithelioma' an anaplastic tumour of the radial nerve in a man aged 35, who later developed tumours in both lungs as revealed by radiographic evidence; the figures show a pleomorphic celled tumour without distinct epithelial characters. In my opinion none of the cases cited was of indubitable nature. Unless very thorough necropsy is performed in such cases the possibility of the nerve tumours being metastatic cannot be excluded. Moreover, it must not be forgotten that compact

years or throughout life. The underlying developmental error is genetic at least in part and though its main effects are visited on nerve sheaths the development of other parts of the nervous system and its envelopes may also be disturbed.

(iii) The development of neurilemmoma of localized progressive fibroma or of neurogenic sarcoma, must be looked upon as a supervention on the original lesion, a supervention to which, however, it is strongly predisposed.

SOLITARY NEUROFIBROMA AND NEUROGENIC SARCOMA

Solitary neurofibromas and neurogenic sarcomas, structurally similar to those of von Recklinghausen's disease, but unaccompanied by any signs of that disease, are relatively common. My own experience includes a benign neurofibroma of the radial nerve in a man aged 21, a small neurofibroma of the oculomotor nerve (reported by Elder), a neurogenic sarcoma of the peroneal nerve of a woman aged 27 and the following case of sarcoma of the radial nerve.

Case IX—History—A man aged 22 noticed a painful rapidly enlarging swelling in his right cubital fossa. This was diagnosed abscess and was incised but no pus was found. Biopsy showed rapidly growing spindle-celled sarcoma. Amputation above the elbow was performed and dissection and microscopical examination showed the tumour to extend diffusely along the radial nerve and to invade neighbouring veins. Death occurred one year later. *Necropsy* showed multiple metastases in both lungs, several bones, retroperitoneal tissues, pelvic lymph glands, scalp and medulla of left adrenal. *Histology*—All tumours showed diffusely infiltrating pleomorphic-celled growth with some distinctly myxosarcomatous areas.

HISTOGENESIS OF TUMOURS OF NERVE SHEATHS

From the foregoing account the following conclusions emerge:

- (i) There occurs a distinctive nerve sheath tumour, usually solitary and benign, the structure of which shows (conclusively, I think) its derivation solely from the neurilemmal cells of Schwann, and which therefore is appropriately called 'neurilemmoma'.
- (ii) Most of the lesions of generalized neurofibromatosis do not show this structure but neurilemmomas may develop in cases of this disease.
- (iii) Benign nerve sheath tumours resembling those of neurofibromatosis and devoid of distinctive neurilemmoma structure also occur as solitary growths.
- (iv) Malignant growths occur as isolated lesions or in cases of neurofibromatosis; these rarely show any evidence of neurilemmomatous structure but occasionally they do so.

Correct concepts of the histogenesis of nerve sheath tumours are of course dependent on correct concepts of the histogenesis of the nerve sheaths themselves. The most widely accepted view has been that the Schwann cells are special ectodermal derivatives of the neural crest and are to be distinguished sharply from the mesenchymal fibroblasts of the endoneurium and perineurium. Studies of the proliferation of Schwann cells in injured nerves and *in vitro* (Mason, Murray and Stout, Murray Stout and Bradley) while showing that these cells probably do possess distinctive characters not shared by mesenchymal cells have shown too that Schwann cells can form collagen. This property is clear also from the structure of neurilemmomas in which all gradations can be traced between typically

- Nelson A A Fitzhugh O G Morris H J, and Calvery H O (1942) *Cancer Res*, 2 11
- Nieberle K, and Cohrs, P (1931) *Lehrbuch der Spez Path Anat der Haustiere*, p 479 Jena
- Nielsen, A (1942) *Ann Surg* 115 849
- Penfield W (1932) *Cytology and Cellular Pathology of the Nervous System*, Vol 3 p 953
- Plenge K (1928) *Virchows Arch* 269 83
- Quick, D and Cutler, M (1927) *Ann Surg*, 86, 810
- Rosenthal D B and Willis R A (1936) *J Path Bact*, 42, 599
- de Santi P R W (1899) *Trans Path Soc Lond*, 50 234
- Schairer E (1933) *Z Krebsforsch* 40, 30
- SCHERER, H J (1934) 'Untersuchungen über den geweblichen Aufbau der Geschwülste des peripheren Nervensystems' *Virchows Arch* 292 479 (An interesting critical study)
- STEWART, F W, and COPELAND, M M (1931) 'Neurogenic sarcoma', *Amer J Cancer* 15 1235 (A useful study and review)
- Stout A P (1918) *Proc New York Path Soc*, 18 2
- STOUT A P (1935) 'The peripheral manifestations of the specific nerve sheath tumor (neurilemmoma)' *Amer J Cancer*, 24, 751 (A study of 52 tumours with good figures and many references)
- Stout A P (1935) *Amer J Cancer* 25 1
- Stout A P and Murrav, M R (1942) *Revue Canad de Biol* 1, 651
- Turner, O A and Gardner, W J (1938) *Amer J Cancer*, 32 339
- Weber, F P and Bode O B (1934) *Proc Roy Soc Med*, 27 638
- Westphalen H (1887) *Virchows Arch*, 110 29
- WORSTER DROUGHT, C, DICKSON, W E C, and McMENEMEY, W H (1937) 'Multiple meningeal and perineural tumours with analogous changes in the glia and ependyma (neurofibroblastomatosis)', *Brain* 60, 85
- Young G A and Olafson, P (1944) *Amer J Path* 20, 413

polyhedral celled areas of neurogenic sarcomas may simulate anaplastic epithelial growth, but this appearance does not warrant calling the tumour 'epithelial'

TUMOURS OF NERVES IN ANIMALS

Multiple dermal fibromata apparently comparable with human neurofibromatosis, have been described in the horse, dog and deer (Feldman), and Nieberle and Cohrs described and depicted multiple diffuse neurofibromata of the axillary plexus, sympathetic nerves and heart in the ox. Some solitary fibromas and fibrosarcomas in animals also show structural evidence of origin from nerve sheaths. Young and Olafson saw multiple nerve sheath fibromas in a family of brook trout—these tumours had a whorled structure but no nuclear regimentation, so that the authors' diagnosis of neurilemmoma is questionable. Lucke however, saw undoubted neurilemmomas in 76 adult fish belonging to 3 species of snappers, 65 of the fish had solitary tumours, 7 had 2 tumours and 4 had more than 2 tumours each. Nelson *et al* observed neurilemmomas of the ears of rats which had been fed for long periods with crude ergot.

REFERENCES

- BAILLY, P. and HERRMANN, J. D. (1938) Role of the cells of Schwann in the formation of tumors of the peripheral nerves. *Amer J Path* 14 1 (Detailed study of two cases of neurofibromatosis with many excellent figures)
- Banarjee D. N. and Christeller E. (1926) *Virchows Arch* 261 50
- Barton A. D. and Inglis K. (1931) *J Coll Surg Austral* 3 397
- Brandes W. W. (1933) *Arch Path* 16 649
- Cohn I. (1928) *Arch Surg* 17 117
- Coupland S. and Balding D. (1877) *Trans Path Soc Lond* 28 23
- DAVIS F. A. (1940) Primary tumors of the optic nerve (a phenomenon of Recklinghausen's disease). *Arch Ophth* 23 735 and 957
- Elder N. G. (1941) *J Path Bact* 52 266
- Feldman W. H. (1932) *Neoplasms of Domesticated Animals* p. 82 Philadelphia
- Fuller R. H. (1941) *Arch Path* 32 441
- Gardner W. J. and Turner O. (1940) *Arch Neurol Psych* 44 76
- Golden T. and Stout A. P. (1941) *Surg Gyn Obst* 73 784
- Gray A. A. (1933) *Proc Roy Soc Med* 26 1309
- Grill J. and Kuzma J. F. (1942) *Arch Path* 34 902
- Harbitz F. (1932) *Acta Path Microbiol Scand* 9 359
- Hartman H. (1927) *Surg Gyn Obst* 44 308
- Hosoi K. (1931) *Arch Surg* 22 258
- Kovács W. (1927) *Zbl allgem Path* 40 518
- Kräyebuhl H. (1936) *Brain* 59 337
- Lewis D. and Hart D. (1930) *Ann Surg* 92 961
- Lucké B. (1942) *Arch Path* 34 133
- Martiz L. (1933) *Frankfurt Z. Path* 46 119
- Masson P. (1932) *Amer J Path* 8 367 and 389
- Masson P. and Martin J. I. (1935) *Bull Assoc franç Cancer* 27 751
- Meyer R. (1943) *Arch Path* 36 437
- De Morgan C. and Coupland S. (1875) *Trans Path Soc Lond* 26 2
- Müller H. (1933) *Zbl allgem Path* 57 55
- Murray M. R., Stout A. P. and Bradley C. F. (1940) *Amer J Path* 16 41
- Murray M. R. and Stout A. P. (1941) *Anat Rec* 84 275

respectively. The tumours described by Moore (1885) and Chaffey (1885) also were undoubtedly adrenal neuroblastomas. Dalton's case (1885) of 'infiltrating growth in liver and suprarenal' in an infant 6 weeks old is of special interest, because Dalton clearly described and depicted the characteristic arrangement of cells in rosettes in the adrenal tumour, and because in spite of the great size of the hepatic growth as compared with that in the adrenal he suspected the tumour of "originating in the medulla of this organ". The liver affection might then be secondary. An admirable example of scientific caution which some modern writers in this field would do well to emulate!

In spite of correct identification of the nature of the tumours by Marchand in 1891, the erroneous view that they were sarcomas persisted well into the present century. In 1901 Pepper described as "congenital sarcoma of the liver and suprarenal" the syndrome of massive hepatic metastasis from adrenal neuroblastoma, which is now often called "Pepper's syndrome". In 1907, Hutchison laid emphasis on the syndrome of 'suprarenal sarcoma in children with metastases in the skull', he suggested that some of the tumours may have been, not sarcomas, but "malignant hypernephromata", but he did not mention their possible neural origin. So also Tileston and Wolbach (1908), though they observed cell rosettes in a tumour which had produced Hutchison's syndrome, failed to appreciate their significance.

The view of Ribbert and his school that the tumours were 'gliomas' had a deservedly short life. As examples of cases reported as such may be mentioned those of Kuster (1905) and Schilder (1909). Kuster's report is of interest in that in her first case bilateral adrenal tumours were present in an infant 14 weeks old and in her second case the subject was an adult, while Schilder's case was that of an infant only 7 days old with a tumour of the abdominal sympathetic chain. In both Kuster's and Schilder's cases the tumours contained prominent rosettes.

The true nature of the tumours was first recognized in 1891 by Marchand, who likened the tissue of the tumours to that of the developing sympathetic ganglia. This view was more clearly stated by Wiesel (1905) who strongly criticized Kuster's identification of the rosettes as gliomatous, and insisted on their identity with the 'Markballen' of the embryonic adrenal medulla or sympathetic ganglia (see Fig 416). Wiesel also noted that such groups of sympathetic formative cells may be found in the adrenals as late as puberty. A most important paper which finally established the identity of the neuroblastomas was that of Wright (1910) who reviewed previous records, reported several new cases, and gave some beautiful photographs comparing the rosettes and parallel bundles of fibrils seen in the tumours with those seen in embryonic adrenal medulla and sympathetic system. One of Wright's cases was a still born male infant with tumours in both adrenals.

Subsequent contributions of importance include those of Herxheimer and Wahl in 1914. Herxheimer using the Bielschowsky method gave proof for the first time that the fibrils in an adrenal neuroblastoma were fine nerve fibres. His specimen also afforded proof that the fibres arose as outgrowths of the cells and were not formed by sheath cells, since unlike the well differentiated ganglioneuromas the tumour contained no sheath cells, i.e. the

CHAPTER 55

NEUROBLASTOMA AND GANGLIONEUROMA

BY NEUROBLASTOMA is meant a tumour consisting of immature undifferentiated neuroblasts, and by ganglioneuroma is meant one consisting of well differentiated nerve cells and fibres. The two types of growth are not sharply distinct however, many tumours of transitional or mixed structure occur and the two names denote merely the poorly differentiated and the highly differentiated members of the same species, the former rapidly growing and malignant the latter slowly growing and relatively benign. All intermediate gradations of structure and behaviour are observed. Hence while in the several sections of this chapter it will be convenient for descriptive purposes to consider separately the two main types of growth the unity of the entire group of tumours must never be lost sight of.

Contrary to what we might have anticipated, these nerve cell tumours are extremely rare (if indeed they ever occur) in the central nervous system while their most frequent sites of origin are the adrenal glands and the ganglia of the sympathetic system. Although they sometimes appear first in adult life, they are much more frequent in infancy and childhood indeed rivalling the embryonic tumours of the kidney as the commonest form of malignant neoplasm in children. The structure of the incompletely differentiated tumours of this group resembles that of the immature tissue of developing sympathetic ganglia and recognition of this similarity was an important step in our knowledge of the histogenesis of these tumours.

HISTORICAL OUTLINE

(1) Neuroblastoma

The history of the imperfectly differentiated neuroblastomas shows three periods in the first period the tumours were called "sarcomas" in the second period they were regarded as of glial nature and finally their true nerve-cell character was recognized.

Although in the first period the specific nature of the tumour cells as sympathetic formative cells was not known and the tumours were regarded as round celled sarcomas or lymphosarcomas many of the early recorded tumours are readily recognizable. Possibly neuroblastomatous was the tumour described by Morgan (1879) as sarcoma of the scapula in an infant 9 weeks old the left adrenal as well as other viscera contained growth and the sarcomatous tissue showed some parts delicately fibrillated. Certainly neuroblastomatous was the tumour reported by Abercrombie (1880) as 'multiple sarcoma of cranial bones' in a female child aged 4 there was a tumour beneath the left adrenal accompanied by a chain of involved lumbar lymph glands and multiple deposits in other parts of the skeleton as well as the skull. So also Parker's case (1880) of congenital sarcoma of the liver was clearly one of adrenal neuroblastoma with secondary disease of the liver. Abercrombie's and Parker's cases are the first records of the syndromes later described by Hutchison and Pepper

'sympathicoblastoma', 'sympathogonioma', 'gangliosympathicoblastoma' All of these names are correct enough, but of course do not denote different tumours. Rigid classification and nomenclature are impossible because of the wide range of differentiation in different tumours or even in one tumour, as particularly insisted on by Wahl, Robertson, and Blacklock (1934). The only valid objection to the simple name "neuroblastoma" for the entire group of imperfectly differentiated tumours is that, as Wahl's case showed, the tumour cells may sometimes display their potentiality for differentiating into chromaffin cells as well as nerve cells. This, however, is a very trifling defect, which the other names mentioned above do not remedy, and Wahl himself considered "neuroblastoma" the simplest and best name. It may be added here that the number of tumours in which, like Wahl's, chromaffin cell potency is displayed is very small, in the great majority of cases any differentiation displayed is in the direction of the formation of neurones only, i.e. the cells are potential neuroblasts, and the name "neuroblastoma" is unreservedly applicable. The occasional cases in which some of the cells show a supplementary direction of differentiation do not justify additional names.

(2) Ganglioneuroma

Correct identification of nerve cell tumours was of course made first with the well differentiated growths containing easily recognizable nerve cells. Prior to Virchow's classical work on tumours (1863-1867), the term "neuroma" had been applied to all new growths arising from nerves, most of which were of course tumours of the nerve-sheaths. Virchow proposed a distinction between these "false neuromas" and "true neuromas" composed of nervous elements proper. A true neuroma containing nerve cells Virchow proposed to call "neuroma gangliocellulare", though no proven case of this kind had so far been described.

The first clear instance of a nerve cell tumour justifying Virchow's prophetic terminology was that described in 1870 by Loretz, an encapsulated growth of the thoracic sympathetic chain in a woman of 35 years containing well formed unipolar nerve cells and non medullated nerve fibres. This was followed in 1879 by Key's account (inaccessible to me) of a ganglioneuroma of the nose in a man aged 31 years, presumed to have arisen from the infra orbital nerve, and by Weichselbaum's report (1881) of a small well defined ganglioneuroma of the medulla of the adrenal gland in a man aged 76 years. No cases were reported for the next 18 years, until 1898, when Busse described a huge retroperitoneal ganglioneuroma in a boy aged 4 years.

From then on there appeared an increasing number of reported examples of ganglioneuroma, the favourite sites of origin of which were soon recognized to be the sympathetic system and adrenal glands. These were fully reviewed in the papers of Beneke (1901) and Wegelin (1909). An unusual case was that described by Knauss in 1898. A female child aged 3 had many widespread subcutaneous tumours consisting of non medullated and a few medullated nerve fibres and many nerve cells. Knauss found the tumours to be related to small arteries and believed them to have arisen from the perivascular sympathetic plexuses. A similar case was described in 1902 by Beneke and Kredel (cited by Herxheimer).

formation of nerve fibres precedes the development of sheath cells in these neural tumours. Another paper of note was by Landau (1912) who gave a thorough review, added three typical examples (one with bilateral adrenal growths and hepatic metastases in a new born infant), noted the range of structural differentiation in this group of tumours and its correspondence with their degree of malignancy and suggested that the chief period of sympathetic differentiation in late foetal and early post natal life accords well with the time of origin of the tumours and points to their dysontogenetic nature. Robertson's paper (1915) stressed the occurrence of all combinations of, and transitions between, well

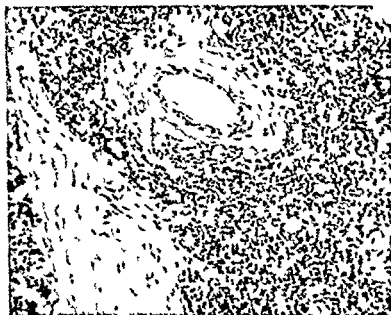


FIG. 416.—Coeliac ganglion of 4 months human foetus showing neuroblastic rosettes ($\times 125$)

differentiated ganglioneuromas and undifferentiated neuroblastomas. Blumensaat (1928) drew special attention to the occasional appearance of neuroblastomas in adults (although Blumensaat's own report is not completely convincing probably owing to the long interval of 48 hours after death before the material was obtained). Bulbring (1928) and Rinscheid (1936) confirmed Herxheimer's earlier finding of the specific staining properties of the young nerve fibres in neuroblastomas. The second worker observing in the tumour cells themselves a fine silver-stainable fibrillary network resembling that seen in normal neuroblasts and stressing the variable degree of neurone differentiation to be seen in these tumours.

Nomenclature

Various workers have proposed elaborate schemes of classification and nomenclature for the tumours according to their degree of differentiation. In addition to neuroblastoma and neuroectoma other names which have been used include the following: sympathoma, embryonale

ganglioneuroma, of weight 1,020 grammes, successfully removed from a woman aged 27, and Cappell's excellent account is accompanied by particularly beautiful microphotographs

AGE INCIDENCE

(1) Neuroblastomas

On the average, neuroblastomas make their appearance decidedly earlier than ganglioneuromas. Collected records (*see for example*, Scott *et al.*, 1933) show that in about one half of reported cases the patients have been less than 2 years old, and at least three quarters of them less than 4 years. In some cases the tumours are known to have been present at birth, even causing dystocia. Wells (1940) has given an excellent review of congenital neuroblastomas, which includes those of Dalton, Richards, Wright, Landau, Fischer, Hagstrom and Rinscheid, as well as 4 cases described by Wells himself.

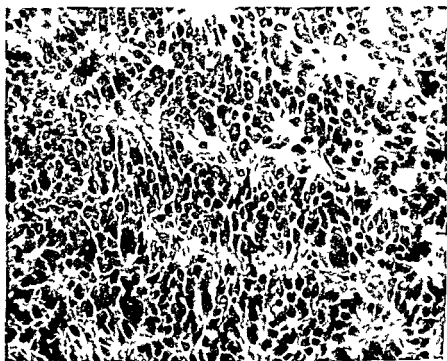


FIG 417—From pulmonary metastases of a primary neuroblastoma of the coeliac ganglion in a man aged 51 showing cells in rosettes and wavy parallel zones with intervening fibrils (*Dr Leila M Hawksley's specimen from Cancer Hospital London*) ($\times 340$)

However, the exact age distribution is still uncertain because the occurrence of adolescent and adult cases has been clearly recognized only within recent years, and such cases are still being misdiagnosed by both clinicians and pathologists e.g. as 'Ewing's tumour' (*see below*). The earlier reviewers of the subject, e.g. Landau and Herxheimer, believed neuroblastomas to occur only in childhood, and the clinical prominence of the striking syndromes first described by Pepper and Hutchison undoubtedly led to overestimation of the frequency of the earlier appearing tumours of this class. A correct estimate of the age distribution of neuroblastomas will be possible only when clinicians and pathologists are much wider awake to the occurrence of adult cases like those reviewed by Blumensaat and like that depicted in Figs 417 and 418 and are much less prone to misidentification of adult and adolescent cases as indicated in my 1940 paper on

A case described by Bruchanow in 1899 resembled Weichselbaum's case in that the tumour was a small well defined nodule in the adrenal gland in an elderly person a woman aged 65. In 1901 Beneke gave a detailed account of 2 carefully studied ganglioneuromas. In the first case one of pelvic ganglioneuroma in a woman aged 25. Beneke noted all transitions between small and large nerve cells observed that the younger cells were aggregated in groups which he regarded as centres of proliferation commented on the frequent presence of multiple nuclei in the cells and concluded that the ganglion cells were the essential neoplastic element in the growth that the nerve fibres were produced by the cells and that the abundant Schwann cells constituted an accompanying stroma to the fibres. Beneke's second case a large retroperitoneal tumour in a girl aged 10 was the first reported instance of a malignant ganglioneuroma with metastases. The bulk of the growth consisted of well differentiated ganglioneuromatous tissue but some areas presented small poorly differentiated cells devoid of fibres and a metastatic deposit in an adjacent lymph gland had a similar undifferentiated structure. Another case of ganglioneuroma with metastases in lymph glands was described by Miller (1908) who saw well differentiated nerve cells and fibres in the secondary growths. In an excellent paper in 1909 Wegelin in describing a large retroperitoneal ganglioneuroma in a girl aged 20 was the first to demonstrate differential staining of neurofibrils in the tumour cells and nerve fibres by the Bielschowsky method.

Falk (1907) was the first writer on ganglioneuromas to support the cell chain theory of the origin of nerve fibres. He believed that in a large retroperitoneal tumour which he examined he could trace the origin of the nerve fibres from the Schwann cells independently of the ganglion cells a belief which his poor illustrations did little to support. The controversy between the neurone and cell chain theories was voiced in many subsequent reports of ganglioneuromas but since the final proof of the correctness of His's neurone theory by the experimental work of Harrison (1908) this controversy is now only of historical interest and may be dismissed by referring to the discussions of it from the pathological aspect by Herxheimer (1914) and Wahl (1914).

In the subsequent development of our knowledge of the ganglioneuromas the following principal landmarks may be mentioned. Herxheimer's paper in 1914 was a most excellent account with a full discussion of all previous reports of ganglioneuromas neuroblastomas and chromaffin tumours and of the histogenetic kinship of the three types. Another comprehensive review in the same year was that of Wahl who also stressed the interrelationship of the three varieties of sympathetic neural tumours and who described an adrenal tumour containing all three kinds of tissue. Robertson (1915) emphasized the occurrence of tumours of transitional or mixed ganglioneuroblastoma structure presenting all possible combinations and degrees of differentiation. Dunn's paper in 1915 was an excellent and succinct account with admirable illustrations. Tumours of transitional and combined type and multiple tumours of the sympathetic system are the subject of another valuable recent paper by Wahl and Craig (1938). The tumour described by Cappell (1929) was a notable example of a large benign retroperitoneal

or adult life and in a few cases small quiescent ganglioneuromas have been discovered incidentally at necropsy in middle aged or old people, e.g. in Weichselbaum's case at 76 years of age. The approximate age distribution may be judged from the following figures. In Herxheimer's review of 25 cases of adrenal ganglioneuromas with ages at the time of operation or death recorded 15 were under 20 years of age 2 were between 20 and 30 4 between 30 and 40, and 4 older. In Wahl's review of ganglioneuromas of all sites 29 out of 47 cases were under 30 years of age.

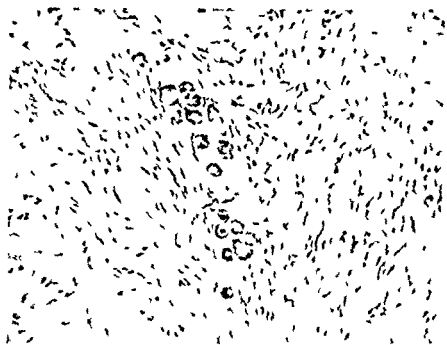


FIG. 419.—*Case 1*. A group of nerve cells in a ganglioneuroma of the thoracic sympathetic chain ($\times 120$).

The following case exemplifies the accidental discovery of a benign quiescent ganglioneuroma.

Case 1.—Routine radiographical examination of the chest of a woman aged 24 prior to her joining the Services showed a well-defined rounded shadow in the left lung field thought to be a hydatid. After 2 years' work in the Land Army without disability, she contemplated marriage and returned for advice. Skiagrams showed no change in the mass which was seen to lie behind the lung. Operation by Mr C. J. O. Brown disclosed an ovoid paravertebral tumour overlying the heads of the 5th to 7th ribs; this was 12 centimetres in main diameter and weighed 16 ounces. To the naked eye it resembled soft oedematous fibrous tissue throughout. Microscopically it consisted of abundant non-medullated nerve fibres accompanied by much fibrous sheath tissue and of scattered small groups of rounded sympathetic ganglion cells (Fig. 419).

In view of the relative benignancy and slowness of growth of these tumours it is clear from the foregoing facts that they must take origin very early in life. It seems probable that their time of origin may be identical with that of the neuroblastomas, that the entire group of tumours is dysontogenetic or embryonic in character, and that they differ amongst themselves only in rate of growth and hence malignancy. Rapidly growing tumours will make their clinical appearance at an early age and will kill speedily; slowly growing well differentiated

Ewing's syndrome No doubt even when this is achieved there will still be a great preponderance of cases in infancy and early childhood but this will certainly be less extreme than is at present supposed

Landau and others have emphasized the general correlation between the age of appearance of the tumours and their degree of histological differentiation and clinical malignancy The earliest appearing tumours are usually the least differentiated most rapidly growing and most speedily fatal Thus tumours producing the Pepper syndrome present at birth or appearing during infancy are usually very rapidly fatal and consist wholly of diffuse round celled growth in which rosette formation is often indistinct or absent Tumours producing Hutchison's syndrome appear on an average a little later often in children between 2 and 8

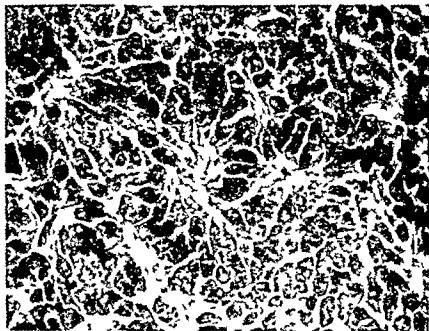


FIG. 418.—Detail of neuroblastic rosettes from the same tumour as Fig. 417 ($\times 500$)

years old are a little less rapidly fatal and consist of tissue which though cellular and rapidly growing frequently shows rosettes and which is sometimes associated with well differentiated ganglioneuromatous tissue in the primary growth (e.g. Cases III and IV below) Neuroblastomas in older children adolescents and adults are often of slower growth (e.g. 4 years known duration in Case VII below) and may show a high degree of rosette and fibril differentiation It must be admitted however that there are many exceptions to the general rule of parallelism between the age of onset and the degree of malignancy of the tumours (see Blacklock)

(2) Ganglioneuromas

As might be expected from their greater differentiation and slower rates of growth ganglioneuromas make their presence known rather later on the average than neuroblastomas While many of them appear during childhood in a considerable proportion of cases their appearance is delayed until adolescence

must be treated with caution, in Blacklock's series the reverse was the case I know of no reported case of bilateral adrenal ganglioneuroma

(2) Multiple primary tumours

While metastasis certainly accounts for some of the bilateral adrenal growths, there is no doubt that primary affection of both adrenals occurs. Thus, Landau observed neuroblastomatous replacement of the medulla of both glands in a new born infant in which the liver was the only other viscus affected, Wright described bilateral adrenal tumours in a still born child, and in Potter and Parrish's case (also recorded by Wells), an 8 months foetus exhibited not only large bilateral tumours involving both adrenals but also widespread neuroblastomatous and ganglion cell tumours of sympathetic ganglia, the vagus nerve, and the wall of the bladder. Pick indeed thought it possible that, since sympathetic cells are widely distributed in the body, multicentric origin might account for secondary growths in other situations, such as the liver and skull, but it is clear that genuine metastasis is responsible for most of the secondary tumours in viscera and bones. Genuinely multiple primary tumours in different parts of the sympathetic system are certainly rare, a typical example is reported by Wahl and Craig who also give other references. Rare cases like those of Knauss, Beneke and Kredel, and Smith, with many subcutaneous ganglioneuromas presumably arising from the perivascular sympathetic nerves, constitute a special group. Smith's case is particularly notable in that the subcutaneous tumours had been present since birth, and necropsy disclosed also an adrenal neuroblastoma.

(3) Neuroblastomas and ganglioneuromas of abdominal viscera

Other than the adrenals and main sympathetic nerves, tumours have been observed in the uterus (Pick, Fingerland and Šikl), mesentery (Jones), intestine (Poate and Inglis), and bladder (Potter and Parrish). Ritter's report of 2 cases of 'neuroblastoma of the intestine' in elderly people is unconvincing, the microphotographs of his first case indeed strongly suggest an argentaftin carcinoma.

(4) Neuroblastomas and ganglioneuromas of the central nervous system

It is very doubtful whether neuroblastomas or ganglioneuromas ever occur in the central nervous system. As to the former, many workers have looked upon the medulloblastomas as 'neurocytomas' or as ambivalent growths representing both neuroblasts and spongioblasts. While this may indeed be the case, the nature of the medulloblastomas is still unsettled (see discussion by Cox, 1933, and also in Chapter 52), and there is certainly no warrant for grouping them and the retinal tumours along with the adrenal and sympathetic neuroblastomas, as Ewing has done. Such an artificial identification of three quite distinct kinds of tumours, merely because they are all malignant, poorly differentiated cellular neural growths occurring early in life, is to be strongly deprecated.

The diagnosis of 'ganglioneuroma' which has been made for occasional tumours of the brain or cord must also be questioned. The first report of this kind was that of Worcester (1901), followed by those of Schminke (1910)

tumours will often have a deferred entrance on the clinical stage and will be less rapidly dangerous or may even remain quite harmless into old age. We will return to this subject later in discussing histogenesis.

SEX INCIDENCE

The sexes differ little, if at all, in their proneness to ganglioneuromas and neuroblastomas. Some series of cases and reviews have suggested a slightly greater incidence in females than in males, e.g. in Herxheimer's review of adrenal tumours, there were 17 female cases of ganglioneuroma to 6 male and 13 female cases of neuroblastoma to 7 male. 25 of 40 cases of ganglioneuroma reviewed by Wahl were in females, Scott and Palmer's review of extra-adrenal neuroblastomas comprised 18 female and 9 male cases and 11 of Blacklock's 18 cases were in female children. However, these numbers are all small and the sex differences not very great and a review by Scott and co-workers of cases of adrenal neural tumours covered 64 males and 53 females. Further collected figures will be necessary to determine whether any real difference of sex incidence exists.

SITES OF ORIGIN

(1) Adrenal glands and sympathetic ganglia

Almost all neuroblastomas and ganglioneuromas demonstrably arise from the adrenal glands or sympathetic nervous system. The adrenal glands are the most frequent single site of origin of these tumours, accounting for about one third of all cases. The abdominal and pelvic sympathetic chains and associated main ganglia, the coeliac and mesenteric ganglia, are the sites of origin of about another third of the tumours, while the remaining third arises from the cervical and thoracic parts of the sympathetic chains or from small peripheral ganglia situated in the viscera themselves. Thus the adrenal glands and abdominal parts of the sympathetic system are the sources of two thirds or more of the tumours, and most of these probably about one half of all tumours arise in the adrenal glands or the great ganglia in their immediate neighbourhood. Available records suggest that ganglioneuromas are somewhat less frequently of adrenal origin than neuroblastomas. Useful reviews of the distribution of the tumours are those of Wahl, Wahl and Craig, Scott and Palmer, and McFarland and Sappington. Reports and reviews of cervical tumours include those of McFarland and Sappington, Land, and Shumacker and Lawrence.

The right and left sides appear to be about equally affected, contrary to the impression obtained by some of the earlier workers from review of the few cases first recorded. Thus in 1909, Wegelin found 14 of 18 recorded sympathetic and adrenal ganglioneuromas to be left-sided, a difference which he suggested might be related in some way to the asymmetry of the embryo. However, larger series of cases show that the difference which impressed Wegelin was fortuitous. Thus of 116 adrenal neuroblastomas reviewed by Scott *et al.* 47 were right-sided, 53 left-sided and 16 bilateral. The figures given by Scott *et al.* suggesting that right-sided adrenal neuroblastomas occur at earlier ages than left-sided ones

a stroma to the neuroblastic or ganglioneuromatous growth, and hence that strictly speaking there are no such tumours as gliomas. Singer and Seiler's descriptions and generally poor photographs will not convince many to their belief, which is mentioned here only as an example of the surprising extremes to which histopathologists can be led by a pet hypothesis and a collection of stains.

COEXISTING DEVELOPMENTAL ABNORMALITIES

Since neuroblastomas and ganglioneuromas take origin during the foetal or early post-natal period, it is pertinent to inquire whether they show any association with other disturbances of development. Such association, I believe, has been observed in only 3 cases, in that of Mittelbach and Szekely and in 2 cases mentioned by Wells. In the first case a male infant exhibited, in addition to a left adrenal neuroblastoma with hepatic metastases, bilateral cleft lip and palate, microcephaly, defective corpus callosum, and patent ductus arteriosus. One of Wells's cases was that of a full-term female foetus with a tiny neuroblastomatous focus in one adrenal, and also hydrocephalus, extensive spina bifida, coarctation of the aorta, patency of the ductus arteriosus, absence of the left ureter, and a malformed rib. In a second case, Wells saw in a slightly premature male foetus, a small neuroblastoma of the right adrenal, and also persistent vitelline duct, vascular anomalies of the brain, and a thymic cyst.

HISTOLOGY

Here it must be recalled that neuroblastomas and ganglioneuromas are not distinct species and that tumours of intermediate and mixed structure frequently occur. We will consider the structure of each of the three varieties in turn.

(1) Neuroblastomas

The most rapidly growing of these tumours, e.g. many of those responsible for the Pepper syndrome and some of those responsible for the Hutchison syndrome, show little or no sign of recognizable neuroblast differentiation; they consist of closely aggregated small rounded or polyhedral cells devoid of arrangement except in so far as this may be determined by the pattern of the tissues infiltrated. The diffusely cellular undifferentiated character of these growths accounts for their having been classed by their first discoverers as "round celled sarcomas". The cells are fairly uniform in size and appearance, being usually 8 to 12 microns in diameter, with scanty ill defined cytoplasm, and each with a single spherical or slightly ovoid nucleus 5 to 8 microns in diameter. Mitotic figures are plentiful.

Less rapidly growing neuroblastomas show various stages in the early differentiation of neuroblasts, namely, grouping of the cells in rosette like clusters and the development of cell processes and young nerve fibres. These fibres constitute the centres of the rosettes or form parallel bundles. In section, each rosette consists of a group of 20 or 30 cells arranged in a ring between 30 and 80 microns in diameter around a central nucleus free fibre zone devoid of a lumen. These rosettes exactly resemble those of developing sympathetic ganglia (compare Fig. 416 with Figs. 417, 418, 423 and 429). The cells forming a well differentiated

Robertson (1915) and others. More recent reviews and additional reports include those of Watjen (1930), Courville (1930 and 1931), Alpers and Grant (1931), Cox (1932) Kernohan *et al* (1932) and Singer and Seiler (1933). The only one of these tumours which I have personally studied is that of Cox whose paper and figures, I think it correct to say, appear to substantiate his diagnosis of 'ganglioneuroma' more convincingly than those of any other contributor in this field and with whose diagnosis I at that time agreed. Yet Cox himself, in the light of further experience, is now fully satisfied that his former diagnosis was incorrect and that his tumour was an astrocytic glioma the cells of which somewhat resembled nerve cells in their structure and staining properties. I have his permission to record his changed opinion which from my own re-examination of his specimen, I share. The following quotation from a later paper by Cox (1933) epitomizes well our reasons for revising our opinion regarding this particular specimen and for rejecting as unproved the diagnosis of 'ganglioneuroma' by the other writers cited above. Speaking of tumours so named Cox says, 'It is probably better at present to preserve an open mind concerning the true nature of many of these tumours. Tumour astrocytes may be exceedingly bewildering not only in their general shape but in the appearance of the nucleus.'

Cells showing a nucleus with a large central nucleolus must not be considered as neuroblastic unless there is undoubted evidence of the presence of neurofibrils and Nissl's bodies. Many of the large protoplasmic tumour astrocytes may also be impregnated with certain of the silver stains, and if the cytoplasm contain granular degeneration products they may suggest by their appearance the presence of Nissl bodies. Cox also stresses the frequent inclusion of non neoplastic cells both nerve cells and glial cells, in the tissues of brain tumours—a further possible source of error in the identification of growths of uncertain nature.

For the foregoing reasons, I find all the reports which I have read of 'ganglioneuromas' of the central nervous system unconvincing. I believe that most of these tumours were gliomas usually large celled astrocytomas in which resemblance of some of the cells to nerve cells in appearance and staining properties has been wrongly construed as identity, or in which included nerve cells have been mistaken for tumour cells. Too much reliance has been placed on supposedly 'specific' stains, silver impregnation methods in particular are very fickle especially when applied to the highly variable tissues of tumours and to necropsy material. The haphazard use of one 'specific' method applied to only a few sections of a tumour has too often been the practice. He who believes he has a specimen of ganglioneuroma of the brain must competently apply a variety of staining methods with appropriate controls, he must very critically evaluate his results, and he must present photographic evidence of the validity of his conclusions as clear and unmistakable as that afforded by specimens of sympathetic ganglioneuromas like those of Dunn, Cappell and others. Nothing short of such complete demonstration can prove the existence of a central ganglioneuroma. The nerve-cell-containing growth of the third ventricle reported by Le Marquand and Russell as a hamartoma and not a true tumour.

It is relevant to refer here to the arresting view of Singer and Seiler (1933) that the essential tumour parenchyma of all gliomas consists of immature or mature nerve-cell tissue that all neuroglial elements in brain tumours are merely

sympathetic ganglia and may be surrounded by satellite or mantle cells (Cappell). The cells commonly occur in large or small groups interspersed amongst the bundles of fibres.

(b) *The nerve fibres* (Figs 419, 422, 425, 427)

These occur in irregular tangles or more often in interlacing well defined bundles measuring up to 0.5 millimetre or more in width. Some bundles consist of fibres only, unaccompanied by neurolemmal cells. Others contain plentiful Schwann cells, and their structure closely resembles that of normal non medullated nerves (Fig 427). Medullated fibres are abundant in only a minority of tumours. The nerve fibres can be stained specifically by the Bielschowsky, Ranson, Bodian or Cajal methods (Fig 422). The fibres may appear to be excessive in comparison with the number of nerve cells in the tumour (Cappell).

(c) *Connective tissue stroma*

This varies in amount. It is often scanty, consisting only of blood vessels with their perivascular tissue penetrating the growth and of fine collagenous strands accompanying bundles of nerve fibres. Less commonly, as in Cappell's tumour, it is more abundant and may become oedematous. The fibrous fasciculated appearance of ganglioneuromas on section is due more to their bundles of nerve fibres than to their connective tissue content. Collections of leucocytes may be present, especially in degenerated areas. In one of my specimens, plasma cells were plentiful in nerve fibre areas.

(d) *Degeneration*

Degenerative changes are common enough in the more malignant tumours of this group, but are not usually prominent in well differentiated ganglioneuromas. It affects chiefly single cells or small groups of cells and leads to a fine granular, rarely massive, calcification. Specific stains may reveal signs of degeneration in some of the nerve fibres in the form of varicosities or end bulbs. Fluid cysts occasionally develop in ganglioneuromatous tissue, as in Jones's case.

(3) *Tumours of transitional or mixed structure ('ganglioneuroblastomas')*

Many of the tumours called ganglioneuromas should really be included in this group, since they show varying degrees of obvious immaturity and proliferative activity of some of their cells. Beneke (1901) was the first to recognize this transitional character, which was later emphasized by Wahl, Robertson, Dunn, McFarland and Sappington and Wahl and Craig. The following possibilities are realized in different specimens of these growths. (i) Parts or the whole of a tumour may show transitional or incompletely differentiated structure, abounding in cells intermediate between neuroblasts and ganglion cells. All degrees of differentiation may be seen in one tumour, ranging from rosettes to fully formed nerve cells and fibres. (ii) A tumour predominantly neuroblastomatous may show differentiation of young nerve cells in places (see Bulbring, Capon, and Fig 417). Cushing and Wolbach recorded a tumour which initially neuroblastomatous, attained increased differentiation later. (iii) A predominantly ganglioneuromatous tumour may contain more or less immature neuroblastomatous tissue, and the latter may outgrow and invade the former, metastases are of neuroblastomatous

rosette are often pear shaped with their stalks directed centrally to become the young nerve fibres of the centre of the rosette. Increasing differentiation renders this fibrillar structure more distinct and produces also strands of parallel fibres which now stain specifically as nerve fibres. Still further differentiation makes the cells more like nerve cells and the tumour now occupies a borderline position between neuroblastoma and ganglioneuroma. All these changes have their counterparts in the differentiation of normal foetal sympathetic ganglia. Stromal connective tissue is scanty in neuroblastomas and no distinct Schwann cells occur in them.

As with other classes of tumours, different parts of a neuroblastoma may show different degrees of differentiation. A tumour, the bulk of which is diffusely cellular and unidentifiable from its structure, may show distinct rosettes in one region only. Usually this is in the primary growth but sometimes a metastasis may show it distinctly as in the following case.

Case II (Willis 1934 No. 297)—A girl aged 13 years had suffered from abdominal enlargement and cachexia for 9 months before her death. *Necropsy* showed a huge left adrenal tumour invading surrounding organs and discrete metastases in liver, lungs and ribs. *Histology*—The bulk of the growths showed a diffuse round-celled structure but rosette formation was visible rather indistinctly in parts of the adrenal tumour and much more distinctly in some of the hepatic metastases.

(2) Ganglioneuromas

The degree of cellular differentiation in ganglioneuromas varies. Many of the tumours so designated contain plentiful immature proliferating cells and belong strictly speaking in the group of intermediate tumours discussed below.

In pure fully differentiated benign ganglioneuromas like those of Loretz, Weichselbaum, Wegelin, Stewart and Cippell the cells closely resemble normal nerve cells and there are plentiful bundles of normal looking non-medullated fibres accompanied by Schwann cells. In the more common less completely differentiated tumours many of the cells though unmistakably nerve cells show various abnormal or immature forms and the fibres are less perfectly organized into bundles and less regularly accompanied by neurolemmal cells. Let us consider in turn the nerve cells, the nerve fibres, the connective tissue stroma and degenerative changes observed in ganglioneuromas.

(a) *The nerve cells* (Figs. 419-421, 425 and 426)

These range from 15 to 100 microns or more in main diameter. They are ovoid, pyriform, pyramidal or irregular in shape and have one, two or more processes. Nuclei measure up to 20 microns or more in diameter; they are most frequently single but cells with multiple nuclei, even 10 or 12 or more are common. Each nucleus usually has a single prominent nucleolus. Mitotic figures which may be plentiful in the small immature cells of actively growing ganglioneuromas are not seen in large well-differentiated cells. The cytoplasm may appear dense and nearly homogeneous or finely or coarsely granular. Appropriate stains may sometimes display typical Nissl's granules and intracellular neurofibrils (see Cippell's beautiful photographs). Quite commonly brown pigment is visible in the cytoplasm of some of the cells. In highly differentiated tumours the ganglion cells may closely resemble those of normal

between neuroblastoma and ganglioneuroma. Most of the neuroblastomatous tissue was diffusely cellular and devoid of rosettes but in some places large well developed rosettes with plentiful central fibres were present. The areas of intermediate structure consisted of pleomorphic cells 15 to 20 microns in diameter some of which showed multiple nuclei and others mitotic figures. All transitions could be traced between these and the less differentiated neuroblastomatous cells but in the sections studied no transitions to the fully differentiated ganglioneuromatous tissue were seen. It was clear that the latter had suffered invasion by the more cellular active growth which penetrated into bundles of nerve fibres and into the bodies of large ganglion cells and in these

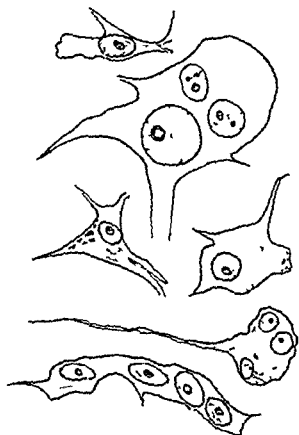


FIG 421—Case III Drawings of individual cells from same section as Fig 420 showing characters of nuclei and Nissl's granules in some cells ($\times 600$)

areas iron haematoxylin staining revealed varicose degeneration of fibres and the formation of end bulbs. The metastatic growths consisted mainly of diffuse neuroblastomatous tissue with occasional imperfect rosettes but in some of them especially in the pulmonary and skull metastases there were areas of transitional structure with pleomorphic cells. No well formed ganglion cells were found in the metastases.

Case IV—A boy aged 2 years was admitted to hospital with a brief history of paresis of the legs and swelling of the eyelids. Examination showed multiple soft swellings on the skull which led later to proptosis of the right eye. Skiagrams showed erosions of the outer table of the calvarium and also patchy rarefaction and periosteal onion skin markings of the shafts of the bones of both legs and both humeri giving appearances which the radiologist stated were identical with those of Ewing's tumours. *Necropsy* (by Dr John Fulton of Launceston Tasmania) 3 months later showed in the right adrenal gland a firm white well defined ovoid tumour 2.3 centimetres in main diameter clothed by a thin layer of adrenal cortex. The left adrenal was normal. The retro peritoneal lymph glands were enlarged by soft white growth and a mass of similar growth

type, though they may show some degree of nerve cell differentiation (Compare the cases of Beneke Miller Berner, Jones, Dunn Wollstein and Heinrich) The following 3 cases illustrate these and other features in the structure and behaviour of these tumours

Case III—A boy aged 4 was admitted to hospital because of pain in the hip and refusal to use the limb Examination showed no abnormality of the hip but there was a palpable left upper abdominal mass Operation disclosed a large inoperable retro peritoneal growth surmounting and involving the left kidney X ray treatment gave no relief and the child died 3 months later *Necropsy* showed a large lobulated growth 15 centimetres in diameter enveloping and invading the upper pole of the kidney and tail of the pancreas infiltrating the psoas muscle and fusing with tumour deposits in

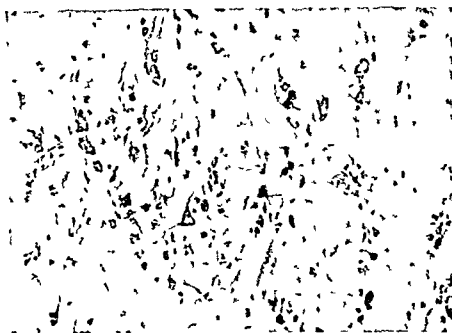


FIG. 420—*Case III* Well differentiated part of retroperitoneal ganglioneuroma (Nissl's stain) ($\times 85$)

neighbouring lymph glands The left adrenal gland was firmly fused to the growth but intact On section parts of the periphery of the growth consisted of firm fibrous fasciculated tissue with a smooth encapsulated surface while the remainder consisted of soft white growth with areas of yellow degeneration Many of the abdominal lymph glands were enlarged by soft growth and there were multiple discrete metastases in the lungs liver right kidney right adrenal skull vertebrae and ribs In the skull the tumours formed large bosses affecting both the calvarium and the base The ribs showed fusiform swellings in which the shafts of the bones were intact but soft growth replaced the marrow and expanded the periosteum away from the bone Vertical rays of new formed bone projected from the bone surfaces into the subperiosteal masses of growth. *Histology* (Figs 420-423)—The fibrous-looking areas of the primary tumour showed well differentiated ganglioneuroma with groups of large nerve cells and many well formed bundles of non medullated fibres accompanied by plentiful Schwann cells Some of the nerve cells gave characteristic tigroid staining by Nissl's method and the nerve fibres stained specifically by Cajal's silver pyridine method Some of the nerve cells were multinucleated but no mitoses could be found in them The soft parts of the growth consisted of neuroblastomatous tissue with some areas intermediate in structure

similar growths. Skiagrams of pieces of ribs and skull showed that the tumours were traversed by bony spines projecting vertically to the surfaces of the affected bones (Fig 424). *Histology* (Figs 425-426)—The bulk of the right adrenal growth had the structure of a well differentiated ganglioneuroma with groups of large nerve cells and bundles of non medullated fibres partly with and partly without accompanying neurolemmal cells. Some areas of the tumour however consisted of tissue of varying degrees

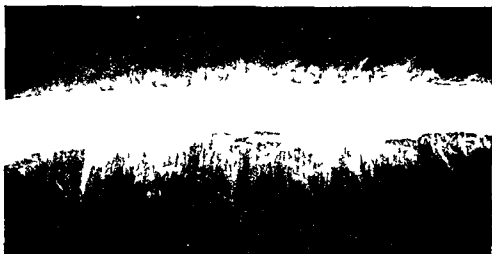


FIG 424 —Case IV Skiagram of piece of skull showing spines of new bone projecting vertically from both inner and outer tables ($\times 3$)



FIG 425 —Case IV Areas of imperfectly differentiated ganglioneuromatous cells and bundles of non medullated nerve fibres ($\times 70$)

of immaturity including round-celled neuroblastic tissue with rosettes and pleomorphic celled tissue showing all stages of transition between the neuroblastic and ganglioneuromatous cells. All of the other growths consisted of immature cells of neuroblastomatous or transitional type the latter forming extensive areas of pleomorphic cells often

5 centimetres in diameter occupied the paravertebral tissues around the body of the third lumbar vertebra. The liver contained many large soft tumours and a single small nodule

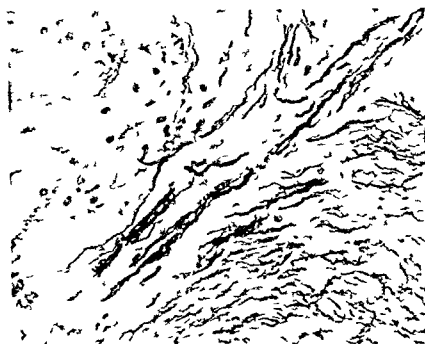


FIG. 422—Case III. Neuraxons in tumour selectively stained by Cajal's pyridine silver method ($\times 450$)

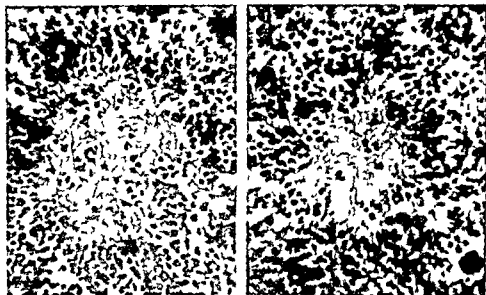


FIG. 423—Case III. Rosettes with fibrils in neuroblastomatous part of tumour (Iron haematoxylin stain) ($\times 300$)

lay in the tail of the pancreas. The ribs and skull showed many large growths, those in the calvarium forming smooth soft bosses projecting both externally and internally and confined by the pericranium and dura mater. The sphenoid and orbital bones showed

as with so many other classes of neoplasms, all of the tumours constitute a single histogenic species, the individuals of which display a wide range of structure and behaviour. At one extreme lie the early appearing highly malignant, poorly differentiated "pure" neuroblastomas, at the other extreme lie the late appearing benign perfectly differentiated "pure" ganglioneuromas, in between the two extremes lie many tumours of "mixed" structure and of varying degrees of malignancy.



FIG. 427—Case V Well differentiated nerve bundles with abundant Schwann cells ($\times 110$)

HISTOGENESIS AND MODE OF GROWTH

From what has already been said it will be evident that our knowledge of the origin of the sympathetic neuroblastomas and ganglioneuromas is in certain respects clear and definite. These growths take origin from the undifferentiated proliferating neural tissue of developing sympathetic ganglia or the adrenal medulla, they are truly embryonic tumours, for they arise from immature formative tissue which has never attained complete adult differentiation. Most of them the neuroblastomas continue to consist of immature cells the proliferation of which goes on progressively at the embryonic or formative level and which never reach the differentiated quiescent state, while a few of them, the ganglioneuromas, grow more slowly and undergo, wholly or in part, differentiation into easily recognized nerve cells and fibres. In neuroblastomatous tissue, as in the foetal sympathetic ganglia the first recognizable stage in neurone differentiation is the appearance of rosette like clusters of cells around small central zones of fine nerve fibres and subsequent stages in the differentiation of the tumours resemble those seen in the normal development of the sympathetic system. In spite of the

multinucleated and with abundant mitotic figures. None of the metastatic growths contained any well formed ganglion cells.

Case V—In April 1938 a male child aged 18 months was admitted to hospital because of abdominal pain and constipation for several days. Examination revealed a large hard mass occupying the pelvis and lower abdomen and laparotomy disclosed a bulky well defined inoperable retroperitoneal tumour fixed to the anterior surface of the sacrum. Microscopical examination of an excised piece of the tumour showed a mixture of ganglioneuromatous transitional and neuroblastomatous structure. Ganglioneuroma predominated but tissue of all degrees of immaturity was mingled with it including young pleomorphic nerve cells and small rounded neuroblasts with rosette formation.

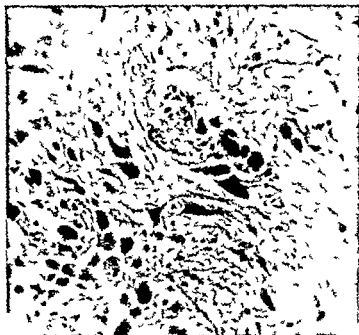


FIG. 426.—Case IV. Detail of Fig. 425 ($\times 230$).

Bundles of well formed nerve fibres with Schwann cells were plentiful at the periphery of the tumour (Fig. 427). *Progress*—Deep X ray treatment was given with benefit and in November 1938 the tumour was palpably smaller and harder and skiagrams showed some calcification in it. In April 1939 constipation again became troublesome and the mass had enlarged again and was compressing the rectum. Further X ray treatment was given with benefit and in August the tumour had become smaller and impalpable abdominally though it could be easily felt per rectum. In April 1940 it had again become palpable abdominally and rectally it was found that the pelvis was almost filled by a hard mass. Further X ray irradiation was followed by some diminution of the mass which then remained but little altered during the next 3 years. By May 1943 however there was some oedema of the lower limbs and the growth again nearly filled the pelvis.

The three primary tumours just described are all malignant, and display a mixture of ganglioneuromatous and neuroblastomatous tissue. In Case III the latter has outgrown and is invading the former while in Cases IV and V the tumours show cells of all grades of differentiation and there is no evidence of invasive substitution of one component by another. From these and other reported cases it is clear that these growths are as much neuroblastomas as ganglioneuromas and that sharp distinction between the two types of growth is impossible. Here,

While it is probable that on the one hand an actively growing tumour may undergo retardation of growth and diminution or loss of malignancy, it is certain on the other hand that acceleration of growth with structural de differentiation and enhanced malignancy is a more common event, active neuroblastomatous growth overtaking and invading a relatively well differentiated ganglioneuromatous tumour (*see Case III above*)

METASTASIS OF NEUROBLASTOMAS

Neuroblastomas, whether arising *de novo* or by de differentiation in pre existing ganglioneuromas, are highly malignant growths with powers of wide dissemination. In most cases the primary growth, usually in the adrenal or abdominal sympathetic system, is small and symptomless and the first or only symptoms are due to metastases in the liver or bones. So striking are some of these metastatic syndromes that they have been given eponyms. Thus Pepper's syndrome denotes great hepatic enlargement due to secondary deposits of neuroblastoma. Hutchison's syndrome denotes the presence of prominent skull metastases, and, as Colville and I first showed (1933), and as I confirmed in 1940 some cases at least of Ewing's syndrome are due to clinically obtrusive metastases of neuroblastoma in long bones. Neuroblastoma metastases may occur in almost any organ or tissue, but so frequent and so clinically important are hepatic and skeletal deposits, that we will consider these separately

(1) Metastases in the liver

True blood-borne metastases appear as multiple discrete rounded white or haemorrhagic growths, which may become very numerous, large and confluent. Direct invasion of the liver, which occurs most frequently from right sided adrenal growths, should be distinguished from true metastases, though it may co exist with these. In either case enormous hepatic enlargement may result, e.g. in a case of Richards to 1,850 grammes in an infant 2 weeks old, in one of Blacklock's cases to 105 ounces (nearly 3,000 grammes) in a child aged 3½ years, and in Dunn's case to 7,290 grammes at the age of 14. Great hepatic enlargement is most often seen in young children or infants, not seldom being noticed at birth or soon afterwards (Pepper's syndrome). Microscopically the deposits in the liver are often more anaplastic than the parent growth and show less distinct rosette formation, but in some cases rosettes are well formed in the metastases (e.g. Case II above).

(2) Metastases in bones

These are very frequent, probably occurring in the great majority of fatal cases, though not always clinically obvious. They are also often much more widespread in the skeleton than might appear from clinical evidence or casual post mortem examination. Thus in cases with Hutchison's syndrome although main attention is naturally focused on the obtrusive skull tumours, careful radiography or dissection of the skeleton will almost always disclose less conspicuous involvement of many other bones, as in Webster's case and in Case IV above. So also the following cases both of which presented the syndrome of

truly embryonic dysontogenetic character of the tumours they are unlike the embryonic retinal tumours in showing no hereditary or familial tendency

There is general agreement that fully differentiated nerve cells are incapable of multiplication. If this is so then neuroblastomas and ganglioneuromas cannot arise from adult sympathetic or adrenal tissue. It is therefore pertinent to inquire at what foetal or post natal age proliferation and differentiation of formative sympathetic and adrenal neural tissue cease for this will determine the age limit for the possible origin of these tumours. According to Wiesel (1902 and 1905) the formative cells, sympathogonia from which the adrenal medulla develops begin to invade the anlage of the cortex during the eighth embryonic week and subsequently collect centrally and this migration continues throughout foetal life and for some time after birth perhaps even until puberty. According to Poll (1905), the development of ganglion cells from sympathogonia continues until the tenth year. Theoretically then neuroblastic tumours could arise at any time prior to the tenth or twelfth year of life though we might expect the majority to do so during the foetal or infantile period when cellular proliferation is most vigorous. The age incidence of neuroblastomas and ganglioneuromas accords well with this expectation, as we have seen many neuroblastomas are known to be present at birth or soon afterwards and even the more slowly growing ganglioneuromas frequently make their appearance during childhood or adolescence.

The incapacity of adult nerve cells for proliferation has an important bearing also on the mode of growth of established ganglioneuromas. As Wahl and others have pointed out and as I can confirm well differentiated nerve cells in these tumours do not participate in proliferative growth. Embryonic neuroblasts and immature nerve cells are the proliferating elements and every growing tumour contains such cells in varying numbers and shows transitional forms between these and the fully developed ganglion cells. Strictly speaking then every ganglioneuroma still exhibiting any proliferative growth is really a transitional or mixed tumour as described above a ganglioneuroblastoma and the only tumours fully entitled to be called benign ganglioneuromas are those relatively rare completely quiescent tumours sometimes seen in adults such as those described by Weichselbaum and Bruchanow and my Case I.

A most interesting point discussed at some length by Wells is the possibility of an initially neuroblastomatous growth undergoing maturation and loss of malignancy with the passage of time. Clearly all nerve-cell tumours must be neuroblastomas at their inception even those which later attain relatively benign ganglioneuromatous differentiation. Indefinite retention of vigorous neuroblastic proliferation is the mark of a malignant neuroblastoma. The theoretical possibility that such a growth may later cease to proliferate and may differentiate into a quiescent ganglion-cell tumour appears to have been realized in the case recorded by Cushing and Wolbach in which a paravertebral neuroblastoma in a child 2 years old retrogressed and exploratory operation 10 years later disclosed a small residual mass with the structure of an inactive ganglioneuroma. Wells cited other instances suggesting the possible cessation of growth and benign conversion of neuroblastomatous tumours and maturation of the tumour may have occurred also in Eden's Case 2. Needless to say careful follow up of such cases is essential before reaching final conclusions as to the sequence of events

While it is probable that on the one hand an actively growing tumour may undergo retardation of growth and diminution or loss of malignancy, it is certain on the other hand that acceleration of growth with structural de-differentiation and enhanced malignancy is a more common event, active neuroblastomatous growth overtaking and invading a relatively well differentiated ganglioneuromatous tumour (see Case III above)

METASTASIS OF NEUROBLASTOMAS

Neuroblastomas, whether arising *de novo* or by de-differentiation in pre-existing ganglioneuromas, are highly malignant growths with powers of wide dissemination. In most cases the primary growth, usually in the adrenal or abdominal sympathetic system, is small and symptomless and the first or only symptoms are due to metastases in the liver or bones. So striking are some of these metastatic syndromes that they have been given eponyms. Thus Pepper's syndrome denotes great hepatic enlargement due to secondary deposits of neuroblastoma, Hutchison's syndrome denotes the presence of prominent skull metastases and, as Colville and I first showed (1933), and as I confirmed in 1940, some cases at least of Ewing's syndrome are due to clinically obtrusive metastases of neuroblastoma in long bones. Neuroblastoma metastases may occur in almost any organ or tissue, but so frequent and so clinically important are hepatic and skeletal deposits, that we will consider these separately

(1) Metastases in the liver

True blood borne metastases appear as multiple discrete rounded white or haemorrhagic growths, which may become very numerous, large and confluent. Direct invasion of the liver, which occurs most frequently from right sided adrenal growths, should be distinguished from true metastases, though it may co-exist with these. In either case enormous hepatic enlargement may result, e.g. in a case of Richards to 1,850 grammes in an infant 2 weeks old, in one of Blacklock's cases to 105 ounces (nearly 3,000 grammes) in a child aged 3½ years, and in Dunn's case to 7,290 grammes at the age of 14. Great hepatic enlargement is most often seen in young children or infants, not seldom being noticed at birth or soon thereafter (Pepper's syndrome). Microscopically the deposits in the liver are typically anaplastic than the parent growth and show less distinct rosette structure. In some cases rosettes are well formed, typical and unlikely to be mistaken for anaplastic tissue. In many cases the deposits are typical and unlikely to be mistaken for anaplastic tissue. It is notable that "onion skin" laminae have been seen in many of the recorded cases of "Ewing's sarcoma" of bone, and have been held by some radiologists to be diagnostic of this tumour.

In their later stages metastatic neuroblastoma in bone may spread very widely and diffusely, often eventually involving a long bone for its entire length, producing patchy rarefaction of the medullary bone, eroding the cortical surface and giving it a coarse sand paper texture and breaking through the expanded periosteal sheath to spread irregularly into surrounding soft tissues. In spite of widespread involvement and patchy rarefaction the cortical layer of bone is seldom totally destroyed, and pathological fracture of long bones is unusual.

The route of dissemination of the skeletal metastases is clearly by the blood stream. Section of various parts of the skeleton in cases with such metastases

massive Ewing's tumour of the femur illustrate well the widespread distribution of the skeletal deposits, as well as other features

Case VI (Reported in detail by Colville and Willis 1933 and see Figs 428, 429) — A girl 8 years old had a large fusiform tumour of the right femur which had first been diagnosed as chronic osteomyelitis but which exploratory operation and biopsy showed to be a richly cellular round-celled non-osteogenic tumour. X-ray treatment gave prompt and striking improvement and a confident diagnosis of "Ewing's sarcoma" was made



FIG. 428 — *Case VI* Skiagram (positive print) of femur showing onion skin layers of new bone evoked by metastatic neuroblastoma

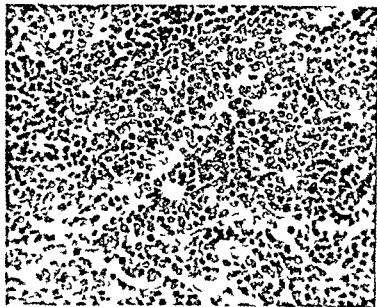


FIG. 429 — *Case VI* Rosettes in primary adrenal neuroblastoma (240)

Necropsy six months from the onset disclosed in addition to the large right femora growth smaller medullary and subperiosteal tumour deposits in the cranial bones mandible all vertebrae all ribs sternum right humerus, clavicles pelvis and left femur. The right adrenal contained a small primary neuroblastoma with distinct rosettes. Multiple discrete metastatic growths were present in the liver lungs both kidneys left adrenal and retroperitoneal lymph glands and microscopic deposits of tumour were also found in the spleen.

neuroblastoma was made. X ray therapy was applied to the fibular tumour and also to the retroperitoneal area. The tumour showed prompt diminution but within four months there was evidence of further disease in the lower half of the fibula and also in the shaft of the femur and severe pelvic pain and oedema of the right leg later developed. Later still a large pelvic mass became palpable, pathological fracture of the femur took place, and the girl died in a private hospital where no necropsy was obtained.

Although in this case necropsy proof of the primary source of the tumour was not available, the close clinical and radiographic similarity to my Cases VI and VII and to Aitken's case cited above, and the histology of the growth, leave little room for doubt as to its nature. (For further discussion of "Ewing's sarcoma", see Chapter 43.)

(3) Metastases in other tissues

(a) *Lymph glands*

Lymph glands are frequently affected, first those adjacent to the primary growth, and then more remote groups. Eventually lymphatic spread may become very extensive, so that a primary abdominal neuroblastoma may produce deposits not only in all retroperitoneal lymph glands but also in the pelvic, inguinal, mediastinal and cervical groups. However, clinically apparent enlargement of these seldom appears until a late stage of the disease. The affected glands are soft, white or haemorrhagic, sometimes discrete, sometimes diffusely fused. Microscopically, rosettes can often be found in parts of the lymph nodal deposits.

(b) *The lungs*

The lungs develop metastases fairly frequently. The precise proportion of cases with dissemination by the blood stream in which metastases appear in the lungs is uncertain. In all 4 cases on which I personally performed necropsies (Cases II, III, VI and VII above), multiple discrete pulmonary metastases were present. On the other hand, in many reported cases with Pepper's syndrome and in some of those with Hutchison's syndrome, no metastases have been observed in the lungs. In Blacklock's 12 cases with complete necropsies, the only lung metastases seen were a few small subpleural nodules in 2 cases, a paucity which Blacklock thought notable in view of the frequent presence of skeletal metastases. However, perhaps careful microscopic search might often disclose non-proliferating tumour emboli arrested in the pulmonary arterioles, as in the well known observations of M. B. Schmidt on cases of abdominal carcinoma.

(c) *Other situations*

Other situations in which discrete metastases have been observed include kidneys, adrenals, spleen, pancreas, ovaries and subcutaneous tissues, most of which are represented in the cases recorded above. Cerebral metastases have not been reported. Peritoneal or pleural involvement has occurred frequently as a result of direct spread from growths in neighbouring organs or lymph glands, and peritoneal deposits in their turn may invade abdominal or pelvic viscera. Direct invasion of the pancreas, kidney, spleen or vertebrae from primary adrenal or lumbar sympathetic tumours occurs frequently.

METASTASIS OF GANGLIONEUROMAS

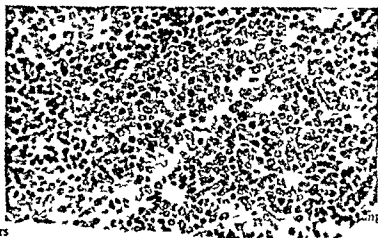
"Malignant ganglioneuromas" with metastases in neighbouring lymph glands have been reported by Beneke, Miller, Berner and others. From what has already

massive Ewing's tumour of the femur, illustrate well the widespread distribution of the skeletal deposits, as well as other features

Case VI (Reported in detail by Colville and Willis 1933 and see Figs 428-429)—A girl 8 years old had a large fusiform tumour of the right femur which had first been diagnosed as chronic osteomyelitis but which exploratory operation and biopsy showed to be a richly cellular round-celled non-osteogenic tumour. X-ray treatment gave prompt and striking improvement and a confident diagnosis of Ewing's sarcoma was made.



FIG 428—*Case VI* Sialogram (positive print) of femur showing onion skin layers of new bone evoked by metastatic neuroblastoma



skin layers

ing and "onion

Microscopically the skeletal growths often lack rosettes and fibrils and show only diffuse round-celled structure. Sometimes however, rosette formation is distinct and may afford strong biopsy evidence of the true character of a bone tumour of otherwise obscure nature, as in the following case:

Case VIII (Dr W. P. H. Iman's case, Launceston, Tasmania)—A girl 14 years old began rather suddenly to suffer from pain and swelling of her right fibula, thought at first to be due to subacute osteomyelitis. After 6 weeks radiographs (Fig 430) showed a fusiform soft tissue mass around the upper half of the fibula containing onion skin markings suggesting Ewing's tumour. At exploratory operation the expanded periosteum was thickened and gritty on incising it, pale soft tissue was found but no pus. A piece removed for microscopic examination showed a round-celled growth with many mitoses but also containing distinct rosettes with central fibrils. Both the cells and rosettes were identical with those of other neuroblastomas examined and a diagnosis of metastatic

- Cox L B (1932) *Med J Austral* 1 347
 Cox L B (1933) *Amer J Path* 9 839
 Curtis M R Bullock F D and Dunning W F (1931) *Amer J Cancer*, 15, 67
 Cushing H and Wolbach, S B (1927) *Amer J Path*, 3 203
 Dalton N (1885) *Trans Path Soc Lond* 36 247
 DUNN, J S (1915) Neuroblastoma and ganglioneuroma of the suprarenal body *J Path Bact* 19 456 (A valuable tabular review, and two interesting case reports with good microphotographs)
 Eden K (1931) *Brit J Surg* 28 549
 Fink F (1907) *Beitr path Anat* 40 601
 Fingerland A and Šikl H (1938) *J Path Bact*, 47 631
 Frew R C (1910) *Quart J Med* 4 123
 Haddow A and Blake I (1933) *J Path Bact*, 36 41
 Heinrichs D (1933) *Zbl allg Path* 58 1
 HERXHEIMER, G (1914) Über Tumoren des Nebennierenmarkes insbesondere das Neuroblastoma sympathicum, *Beitr path Anat* 57 112 (A valuable outline and review of previously reported cases)
 Hutchison R (1907) *Quart J Med* 1, 33
 Jones H M (1912) *Lancet* i 1678
 Kernohan J W Learmonth J R and Doyle J B (1932) *Brain* 55 287
 Knauss K (1898) *Virchows Arch* 153 29
 Kuster H (1905) *Virchows Arch*, 180 117
 Land F T (1935) *Brit J Surg* 23 474
 LANDAU, M (1912) Die malignen Neuroblastome des Sympathikus, *Frankfurt Z Path* 11 26 (An important contribution and review)
 Loretz W (1870) *Virchows Arch*, 49 435
 Marchand F (1891) *Intern Beitr Z Wiss Med* 1 535
 Le Marquand H S and Russell D S (1934-1935) *Royal Berkshire Hosp Rep* p 31
 McFarland J and Sappington S W (1935) *Amer J Path* 11 429
 Miller J W (1908) *Virchows Arch* 191 411
 Mittelbach M and Szekely P (1934) *Frankfurt Z Path* 47 517
 Moore N (1885) *Trans Path Soc Lond* 36 393
 Morgan J H (1879) *Trans Path Soc Lond*, 30 399
 Nieberle K, and Cohrs P (1931) *Lehrbuch der Spec. Path Anat der Haustiere*, p 479 Jena
 Parker R W (1880) *Trans Path Soc Lond* 31 290
 Pepper W (1901) *Amer J Med Sci* 121 287
 Pick L (1912) *Berlin klin Wschr* 49 16 67
 Poate H and Inglis, K. (1928) *Brit J Surg* 16 221
 Poil H (1905) *Hertwigs Handb d Entwickl d Wirbeltiere* Vol III p 443 Jena
 Potter E L and Parrish J M (1942) *Amer J Path* 18 141
 Richards O (1905) *Guy's Hosp Rep* 59 217
 Rinscheid J (1936) *Virchows Arch* 297 508
 Ritter, S A (1925) *Amer J Path* 1 519
 Robertson H E (1915) *Virchows Arch* 220 147
 Salaskin B A (1930) *Z Krebsforsch* 30 371
 Schilder P (1909) *Frankfurt Z Path* 3 317
 Schminke A (1910) *Beitr path Anat* 47 354
 Scott E Oliver M G and Oliver M H (1933) *Amer J Cancer* 17 396
 Scott E and Palmer D M (1932) *Amer J Cancer* 16 903
 Shumacker H B and Lawrence E A (1939) *Surgery* 5 572
 Singer L and Seiler J (1933) *Virchows Arch*, 287 823
 Smith J (1932) *Lancet* ii 1214
 Stewart M J (1919) *J Path Bact* 23 118
 Tileston W and Wolbach S B (1908) *Amer J Med Sci* 135 871
 WAHL H R (1914) Neuroblastoma with a study of a case illustrating the three types that arise from the sympathetic system *J Med Res* 25 205 (A valuable detailed review and thorough study of an unusual case)

been said of the histology and mode of growth of these tumours it will be clear that their proliferation and metastasis must depend on the presence in them of immature neuroblastic cells. Fully differentiated ganglion cells do not multiply and hence a pure ganglioneuroma composed wholly of fully differentiated cells would be incapable of further growth or metastasis. The metastasizing elements of a tumour must be immature proliferating cells, which may or may not attain recognizable nerve cell differentiation in their new sites. As insisted on by McFarland and Sappington any growing nerve-cell tumour containing immature cells must possess some degree of actual or potential malignancy and powers of metastasis. We return, then to the view insisted on at the opening of the chapter neuroblastoma and ganglioneuroma are merely names applied to the poorly differentiated and the well differentiated members of a single class of growths within which all gradations of structure and behaviour are to be observed.

GANGLIONEUROMA AND NEUROBLASTOMA IN ANIMALS

Nieberle and Cohrs referred to a ganglioneuroma in a horse described by Gmelin. They also stated that they had seen a similar tumour of the sympathetic chain with metastases in lungs and muscles in an ox, but they gave no details or figures. Curtis *et al* recorded a ganglioneuroma of the optic nerve in a rat. Ganglioneuromas are probably not very uncommon in fish. Haddow and Blake described a specimen and referred to two others.

In a 6-months old rabbit, Salaskin found a neuroblastoma of the neck with metastases in lungs, liver and spleen. Instead of rosettes the tumour showed sinuous ranks of cells with fibril zones between them—"zebra markings". In a 6-years old cow Baumgartner saw a tumour of the shoulder and presumed secondary growths in the lungs, left kidney and abdominal lymph glands. Microscopically these were said to show mingled neuroblastoma and ganglioneuromatous structure while this diagnosis may have been correct the figures do not convincingly establish it.

REFERENCES

- Abercrombie J (1880) *Trans Path Soc Lond* 31 216
 Arken S G (1942) *N Z Med J* 41 209
 Alpers B J and Grant F C (1931) *Arch Neurol Psych* 26 501
 Baumgartner H (1931) *Z Krebsforsch* 34 174
 Beneke R (1901) *Beitr path Anat* 30 1
 Berner J H (1922) *Beitr path Anat* 70 203
 BLACKLOCK J W S (1934) Neurogenic tumours of the sympathetic system in children
J Path Bact 39 27 (A valuable review with case reports and good illustrations)
 Blumensaat C (1928) *Virchows Arch* 269 431
 Bruchanow (1899) *Z Heilk* 20 40
 Bulbring E (1928) *Virchows Arch* 268 300
 Busse O (1898) *Virchows Arch* 151 (suppl) 66
 Capon N B (1928) *J Path Bact* 31 659
 CAPIELL D F (1929) Retrocervical ganglionic neuroma *J Path Bact* 32 43 (A notable case report with beautiful microphotographs)
 Chaffey W C (1885) *Trans Path Soc Lond* 36 415
 Colville H C. and Willis R A (1933) *Amer J Path* 9 421
 Courville C B (1930 and 1931) *Arch Neurol Psych.* 1930 24 439 1931 25 309

TUMOURS OF CHROMAFFIN TISSUES AND OF THE CAROTID AND AORTIC BODIES

MANY histologists and pathologists now doubt the correctness of the formerly prevalent view that the carotid and aortic bodies are paraganglionic or chromaffin tissues essentially similar to the adrenal medulla. On the contrary, evidence has accumulated (references by Bloom) that these bodies do not secrete adrenaline but are special chemo receptors concerned with the reaction of the blood. Certainly, carotid body tumours differ from the chromaffin tumours of the adrenal medulla in both structure and behaviour. Hence, while both kinds of tumours arise from tissues of neural derivation, they are best considered separately.

CHROMAFFIN TUMOURS OF ADRENAL MEDULLA AND THE ORGANS OF ZUCKERKANDL

(1) Incidence, site and causation

Most chromaffin tumours—or phaeochromocytomas—have been found in young or middle aged adults, and the two sexes appear to be about equally liable. In the majority of cases, the tumours are unilateral and solitary, but bilateral tumours are not rare (Schroder, Rosenthal and Willis, and other references by Edwards). Unequivocal instances of tumours of Zuckerkandl's bodies are very rare, in Cragg's case they were bilateral and associated with a carotid body tumour. The association of chromaffin tumours with neurofibromatosis, as in the cases of Suzuki, Kawashima, Herxheimer, and Rosenthal and Willis, is too frequent to be fortuitous. Staemmler's finding that chronic nicotine poisoning can engender adrenal chromaffin tumours in rats may afford a clue to causation, and further experiments are needed.

(2) Structure

To the naked eye, the tumours appear as well circumscribed, but usually not encapsulated, spherical or ovoid masses of homogeneous grey or brownish tissue. Most of them are less than 5 centimetres in diameter, but some are much larger, e.g. that recorded by Belt and Powell weighed 1,000 grammes. The smaller tumours are usually enveloped by a yellow layer of stretched adrenal cortex. Fixatives containing potassium bichromate or other chromium salts stain the tumours a dark rich brown, like that of the adrenal medulla itself.

Microscopically, the growths show a general resemblance to adrenal medullary tissue consisting of non compact groups of polygonal or irregular cells with intervening vascular channels. There is often much variation in size and shape of the cells, and multiple nuclei and vacuolation of the cytoplasm are both common. Mitotic figures are usually scanty. Cell boundaries are often indefinite. Appropriate stains usually reveal the presence of fat and lipoids. The intensity of the chromaffin reaction varies from tumour to tumour and often from cell to cell of the one tumour. Sevki described apparently specific eosinophilic cytoplasmic

- WAHL H R, and CRAIG P E (1938) Multiple tumors of the sympathetic nervous system
Report of a case showing a distinct ganglioneuroma a neuroblastoma and a cystic calcifying
ganglioneuroblastoma *Amer J Path* 14 797 (Valuable report and review)
- Watson J (1930) *Virchows Arch* 277 441
- Webster R (1939) *Med J Austral* 1 193
- WEGELIN C (1909) Über ein Ganglioneurom des Sympathicus *Beitr path Anat* 46
403 (The best of the earlier reviews)
- Weichselbaum A (1881) *Virchows Arch* 85 554
- WELLS H G (1940) Occurrence and significance of congenital malignant neoplasms
Arch Path 30 535 (An admirable review including a large section on neuroblastomas)
- Wiesel J (1902) *Anat Hefte* 19 481
- Wiesel J (1905) *Virchows Arch*, 180 553
- WILLIS, R A (1940) Metastatic neuroblastoma in bone presenting the Ewing syndrome
with a discussion of Ewing's sarcoma *Amer J Path* 16 317 (A critical review of
Ewing's Tumour)
- Wollstein M (1928) *Surg Gyn Obst* 46 774
- Worcester W L (1901) *J Med Res* 1 59
- WRIGHT, J H (1910) Neurocytoma or neuroblastoma a kind of tumor not generally
recognized *J Exp Med* 12 556 (An important beautifully illustrated paper firmly
establishing the identity of neuroblastomas)

reports of 143 cases, and in 1931 Rankin and Wellbrock a total of 196. Nearly three quarters of the tumours have been in patients between 30 and 60 years old, the mean age is about 42. But, as many of the tumours are known to be of very long duration—20, 30, 35 years or longer—and as they are often of some size when first noticed, the actual age of onset is probably in early adult life in most cases. Males and females are about equally affected. With rare exceptions, the growths are unilateral, but bilateral tumours are recorded by Lund, Rankin and Wellbrock, Chase and others. Chase saw carotid body tumours in two sisters, the only record of familial occurrence. Cragg reported concurrent tumours of the left carotid body and of both organs of Zuckerkandl. Bloom saw two examples



FIG. 431.—Carotid body tumour, showing groups of epithelium like cells separated by vascular spaces ($\times 120$)

of tumours near the base of the heart in dogs, probably derived from the aortic bodies. I know of no instance of such a tumour in man.

(2) Structure

The naked eye appearance is not inaptly described in the simile 'potato tumour'. The growths are smoothly lobulated, encapsulated, firm, homogeneous white or greyish; they usually envelop the arteries at the bifurcation, or the vessels lie in deep grooves in the tumour. In size they vary from 2 to 6 centimetres or more in main diameter.

Microscopically, the tumours consist of masses of epithelioid cells resembling those of the carotid body, separated by vessels or strands of connective tissue (Figs 431, 432). The cells are usually large, polyhedral or irregular, with rather indefinite outlines, with abundant homogeneous or vacuolated cytoplasm in which fat droplets can often be demonstrated. The nuclei are usually single

granulation of formalin fixed tumour tissue and of normal medulla, this method deserves further study. Nerve bundles and nerve cells may be found within the growths, and Rosenthal and I observed chromaffin granules in these nerve cells as well as in the other tumour cells. Marginally there is often absence of clear demarcation between tumour tissue and neighbouring medulla, or the tumour cells mingle with those of the surrounding cortex.

(3) Function

The functional activity of many of the tumours is not only suggested by their general resemblance to their parent tissue and the strong chromaffin reaction of their cells, but is proved by their causing persistent or paroxysmal hypertension and other symptoms of hyperadrenalism, and by assays of tumour tissue for adrenaline. Belt and Powell found an unusually large amount of adrenaline in their tumour—2 grammes per 100 grammes of tissue. Palmer and Castleman found 2 milligrams of adrenaline per gramme of tumour. Vulpian's ferric chloride reaction and other staining and chemical tests for the presence of adrenaline have often been reported as positive (Edwards). There are now many reports of paroxysmal hypertension, pallor, flushing, tachycardia, hyperglycaemia and glycosuria, and other symptoms of sympathetic stimulation in patients with chromaffin tumours (Belt and Powell, Edwards, Palmer and Castleman) and in a few of these cases removal of the tumour has alleviated the symptoms.

(4) Malignant chromaffin tumours

In the great majority of cases chromaffin tumours are benign, growing slowly and neither invading surrounding parts nor metastasizing. King described a case in which there were bilateral adrenal growths and widespread metastases in other organs, but although it is possible that King's diagnosis of 'malignant pheochromocytoma' may have been correct, the smallness and bilaterality of the adrenal tumours raise at least the suspicion that they may have been metastases from some undetected primary growth, and he gave no details of his technique in performing the chromaffin test. The malignant pheochromocytoma reported by Eisenberg and Wallerstein is very questionable; there were large malignant growths in both the lungs and thyroid, the adrenal tumours were bilateral and no details are given as to technique or results of the positive chromaffin reaction which was said to be present. Such details are important in judging the merits of supposedly positive chromaffin tests; this reaction is fickle and in tissues initially fixed in other solutions and not chromated until later it is capable of yielding both false negative and false positive results. None of the few malignant supposedly chromaffin-cell tumours reviewed by Belt and Powell were accompanied by symptoms of hyperadrenalism. Two supposed cases of malignant paraganglioma with metastases reported by Lewis and Geschickter are unacceptable; the reports are scanty and inadequate.

TUMOURS OF THE CAROTID AND AORTIC BODIES

(1) Incidence, site and causation

In 1905 Mönckeberg reviewed 9 previously reported examples of tumour of the carotid body and added 3 new ones. In 1929 Bevan and McCarthy collected

- Cragg R W (1934) *Arch Path* 18 635
 Edwards D G (1937) *J Path Bact* 45, 391
 Eisenberg, A A and Wallerstein H (1932) *Arch Path* 14, 818
 Herzheimer G (1914) *Beitr path Anat* 57 112
 Kawashima K (1911) *Virchows Arch* 203 66
 King, E S J (1931) *J Path Bact* 34 447
 Lewis D, and Geschickter C F (1934) *Arch Surg* 28, 16
 Palmer R S and Castleman B (1938) *New England J Med* 219 793
 Rosenthal, D B and Willis R A (1936) *J Path Bact* 42, 599
 Schroder K (1928) *Virchows Arch* 268 291
 Sevkı K (1935) *Virchows Arch* 294 65
 Staemmler M (1935) *Virchows Arch* 295 366
 Suzuki S (1910) *Berlin klin Wschr*, 47 1623

TO TUMOURS OF CAROTID BODY

- BEVAN, A D and MCCARTHY, E R (1929) 'Tumors of the carotid body', *Surg Gyn Obst*, 49, 764 (A useful review)
 Bloom F (1943) *Arch Path* 36 1
 Chase W H (1933) *J Path Bact* 36 1
 Cragg R. W (1934) *Arch Path*, 18 635
 MONCKEBERG, J G (1905) Die Tumoren der Glandula carotica, *Beitr path Anat* 38 1 (An excellent description and review of the first 12 cases recorded)
 Lund F B (1917) *J Amer Med Assoc*, 69 348
 Rankin F W and Wellbrock, W L A (1931) *Ann Surg* 93, 801

sometimes multiple, mitotic figures are infrequent. The chromaffin reaction, which has often been said to be given by these growths and by the carotid body itself is faint and indefinite and not at all comparable with the intense reaction of the adrenal medulla, for example, Monckeberg depicted it as only a faint diffuse yellow staining in some of the cells. Vulpian's test and other tests for adrenaline are negative, and adrenaline is not found in the tumours by assay. It has often been stated that nerves are not present in carotid body tumours, but Chase found plentiful nerve fibres in his cases.

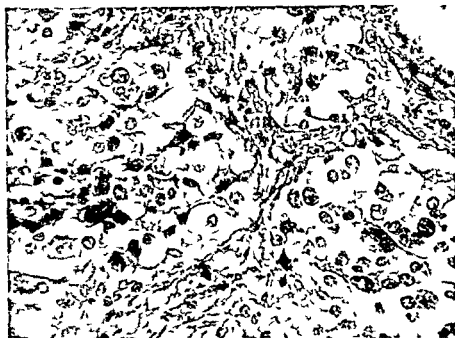


FIG. 432.—Detail of cells of the same tumour as Fig. 431 ($\times 450$)

(3) Malignancy

With few and doubtful exceptions, tumours of the carotid body are benign, growing slowly, remaining sharply circumscribed and producing no metastases. Of some at least of the few recorded cases of supposed malignancy there is room for doubt regarding the identity of the tumours: these may really have been metastatic deposits in the carotid lymph glands from undetected primary tumours elsewhere. The structure of benign carotid tumours is not highly distinctive, and if malignant tumours of this kind occur it is doubtful if they could be distinguished microscopically from metastatic carcinoma. Proof of the primary nature of a suspected tumour will depend on careful necropsy to exclude the possible presence of a primary growth elsewhere. As far as I know, no reported case affords such proof.

REFERENCES

TO CHROMAFFIN ADRENAL TUMOURS

- | | |
|---|--|
| BEIT, A. L., and POWELL, T. O. (1934) | Clinical manifestations of the chromaffin cell |
| tumours arising from the suprarenal medulla | <i>Surg. Gyn. Obst.</i> 59, 9 |

- Cragg R W (1934) *Arch Path* 18, 635
 Edwards D G (1937) *J Path Bact*, 45 791
 Eisenberg, A A and Wallerstein H (1932) *Arch Path* 14, 818
 Herxheimer, G (1914) *Beitr path Anat* 57, 112
 Kawashima K (1911) *Virchows Arch* 203 66
 King E S J (1931) *J Path Bact*, 34 447
 Lewis, D and Geschickter C F (1934) *Arch Surg* 28 16
 Palmer, R S and Castleman B (1938) *New England J Med* 219 793
 Rosenthal D B and Willis R A (1936) *J Path Bact*, 42 599
 Schroder K (1928) *Virchows Arch* 268 291
 Sevkı K (1935) *Virchows Arch* 294, 65
 Staemmler M (1935) *Virchows Arch*, 295 366
 Suzuki S (1910) *Berlin klin Wschr* 47, 1623

TO TUMOURS OF CAROTID BODY

- BFVAN, A D, and McCARTHY, E R (1929) "Tumors of the carotid body", *Surg Gyn Obst* 49, 764 (A useful review)
 Bloom F (1943) *Arch Path*, 36 1
 Chase, W H (1933) *J Path Bact* 36 1
 Cragg R W (1934) *Arch Path*, 18 635
 MONCKEBERG J G (1905) "Die Tumoren der Glandula carotica", *Beitr path Anat*, 38 1 (An excellent description and review of the first 12 cases recorded)
 Lund F B (1917) *J Amer Med Assoc* 69 348
 Rankin F W and Wellbrock W L A (1931) *Ann Surg* 93, 801

CHAPTER 57

NEURO ECTODERMAL TUMOURS OF THE RETINA AND CILIARY BODY

TUMOURS arising from the neural tissues proper of the interior of the eye, i.e. those derived from the embryonic optic vesicle comprise the following

- (A) *Retinoblastomas*, arising from the still imperfectly differentiated optic part of the retina during foetal life or early childhood,
- (B) *True gliomas (astrocytomas)*, arising from the neuroglial cells of the fully developed retina,
- (C) *Epithelial tumours of the ciliary body or iris*, and
- (D) *Rare retinal tumours of other kinds*

Group (A) comprises the great majority of retinal tumours, all of the others are very rare. It must also be noted here that acceptance of Dawson's view that the intra ocular melanomas arise directly or indirectly from the pigment layer of the retina would bring these tumours also within the scope of this chapter. This very distinct class of tumours however, is best considered along with their cutaneous counterparts in Chapter 58.

An understanding of the origins of the retinal tumours requires a clear knowledge of the development of the retina from the optic vesicle—a brief outline of which follows.

DEVELOPMENT OF THE RETINA

Early in the fourth week of development of the human embryo the optic vesicles appear as hollow lateral outgrowths of that part of the primitive neural tube which later becomes the third ventricle. The stalk of the outgrowth is the rudiment of the optic nerve. The vesicle enlarges and becomes invaginated to form the double layered optic cup (Figs 433-435). The outer layer of the cup retains its simple epithelial form and its cells become pigmented to form the pigment layer of the retina. The inner layer of the cup is the rudiment of the sensitive retina. At first this consists of a single layer of neuro epithelial cells but it rapidly thickens by proliferation of its cells the nuclei of which are studded densely throughout it except for a nucleus free zone on its inner or vitreous aspect. The outer surface of the primitive retina is directed towards the pigmented epithelial layer but is at first separated from it by a slit which is all that remains of the cavity of the optic vesicle. Even after this slit is finally obliterated separation in this plane readily takes place as in detachment of the adult retina (Fig 436). From the thickly nucleated embryonic retina all of the cellular components of the retina differentiate namely the outer stratum of sensory rod and cone cells the middle stratum of connecting or bipolar nerve cells the inner stratum of ganglion cells and nerve fibres and also the supporting cells of two kinds, the asteroid neuroglial cells or astrocytes and the vertically arranged sustentacular cells or fibres of Muller. Cellular differentiation and stratification appear first



FIG 433 —Section of 8 mm human embryo showing early optic cup in continuity with floor of brain B = brain L = lens ($\times 90$)

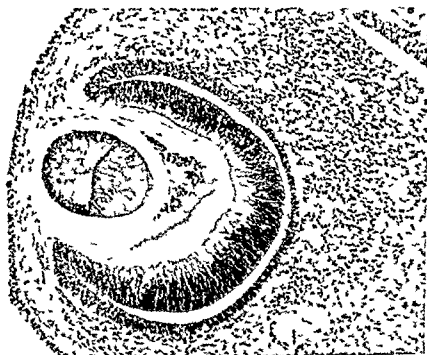


FIG 434 —Section of optic cup of 12.5 mm human embryo ($\times 90$)

at the centre of the optic cup and spread towards the periphery (Fig 435) and by the seventh foetal month differentiation is nearly complete and the retina is sensitive to light. In the fovea and macular area, however, complete differentiation

CHAPTER 57

NEURO-ECTODERMAL TUMOURS OF THE RETINA AND CILIARY BODY

TUMOURS arising from the neural tissues proper of the interior of the eye i.e. those derived from the embryonic optic vesicle, comprise the following

- (A) *Retinoblastomas*, arising from the still imperfectly differentiated optic part of the retina during foetal life or early childhood,
- (B) *True gliomas (astrocytomas)*, arising from the neuroglial cells of the fully developed retina,
- (C) *Epithelial tumours of the ciliary body or iris* and
- (D) *Rare retinal tumours of other kinds*

Group (A) comprises the great majority of retinal tumours all of the others are very rare. It must also be noted here that acceptance of Dawson's view that the intra ocular melanomas arise directly or indirectly from the pigment layer of the retina would bring these tumours also within the scope of this chapter. This very distinct class of tumours however, is best considered along with their cutaneous counterparts in Chapter 58.

An understanding of the origins of the retinal tumours requires a clear knowledge of the development of the retina from the optic vesicle a brief outline of which follows

DEVELOPMENT OF THE RETINA

Early in the fourth week of development of the human embryo the optic vesicles appear as hollow lateral outgrowths of that part of the primitive neural tube which later becomes the third ventricle. The stalk of the outgrowth is the rudiment of the optic nerve. The vesicle enlarges and becomes invaginated to form the double layered optic cup (Figs 433-435). The outer layer of the cup retains its simple epithelial form and its cells become pigmented to form the pigment layer of the retina. The inner layer of the cup is the rudiment of the sensitive retina. At first this consists of a single layer of neuro epithelial cells but it rapidly thickens by proliferation of its cells, the nuclei of which are studded densely throughout it except for a nucleus free zone on its inner or vitreous aspect. The outer surface of the primitive retina is directed towards the pigmented epithelial layer, but is at first separated from it by a slit which is all that remains of the cavity of the optic vesicle. Even after this slit is finally obliterated separation in this plane readily takes place as in detachment of the adult retina (Fig 436). From the thickly nucleated embryonic retina all of the cellular components of the retina differentiate namely the outer stratum of sensory rod and cone cells the middle stratum of connecting or bipolar nerve cells the inner stratum of ganglion cells and nerve fibres and also the supporting cells of two kinds the asteroid neuroglial cells or astrocytes and the vertically arranged sustentacular cells or fibres of Muller. Cellular differentiation and stratification appear first

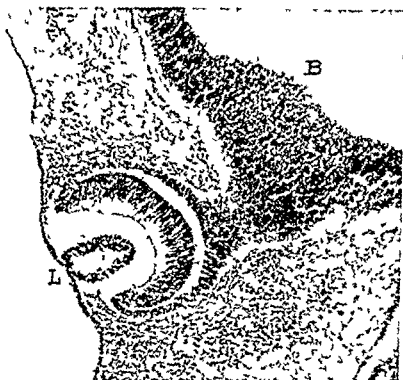


FIG. 433—Section of 8 mm human embryo showing early optic cup in continuity with floor of brain B = brain L = lens ($\times 90$)

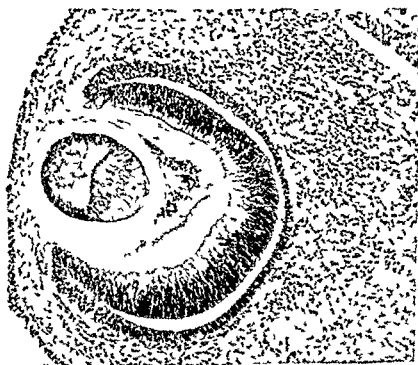


FIG. 434—Section of optic cup of 12.5 mm human embryo ($\times 90$)

at the centre of the optic cup and spread towards the periphery (Fig 435), and by the seventh foetal month differentiation is nearly complete and the retina is sensitive to light. In the fovea and macular area, however, complete differentiation

is not attained until the fourth month after birth. The epithelium of the ciliary body and of the posterior surface of the iris represents the lip of the optic cup and the extreme periphery of the inner layer of the cup, and the insensitive ciliary part of the retina retains a primitive columnar or partly transitional kind of epithelium which is demarcated from the sensitive retina by the ora serrata.

It is relevant to note here the discovery of experimental embryologists that pieces of embryonic retina are capable of almost perfect self differentiation when isolated from their normal connexions and transplanted to other parts of the

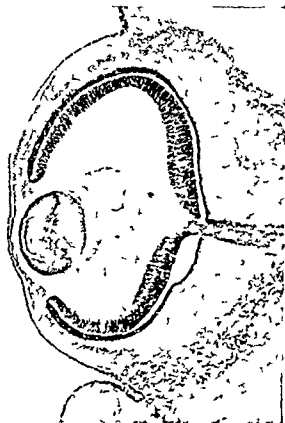


FIG. 435.—Section of optic cup and stalk of 28 mm. human embryo showing early stratification of retina proper and dense pigmentation of outer layer of cup ($\times 52$.)

body (Lewis 1908) or cultivated *in vitro* (Strangeways and Fell 1926). This makes it less surprising that almost perfect differentiation of rosettes of rod and cone cells or even of stratified retina like layers should be seen under the abnormal anatomical conditions prevailing in masses of tumour tissue.

RETINOBLASTOMAS

HISTORICAL OUTLINE

In their advanced stage of fungation on the face the retinal tumours of infancy and childhood are so distinctive and horrible that their recognition as a clinical entity long preceded their pathological study. In the latter half of the eighteenth century they figured among the cases of *fungus haematodes* of the British

are recorded (Wells). In at least two thirds of the cases the tumours are discovered before the age of 3 years, and it is very rare indeed for them to be discovered after the age of 6. In Wintersteiner's large series, 314 of 467 cases (i.e. 67 per cent) were under the age of 3 when the disease was first recognized; in 34 cases (7 per cent) it was known to be pre-natal, and in only 10 cases did the disease appear after the ninth year, the oldest patient being 16. In the Moorfield's series of 163 cases, the oldest was 7 years of age. In a most exceptional case reported by Maghy, one eye was enucleated in the second year, failure of vision began in the remaining eye in the thirteenth year, and this eye was removed at the age of 20. An ocular tumour which first appears after childhood is almost certainly not a retinoblastoma.

(3) Sex incidence

Males and females are about equally affected; of the 759 cases of known sex reviewed by Berrisford, there were 398 males and 361 females.

(4) Influence of the position in the family

Hemmes, Lange and others have given figures suggesting that first-born children are the most prone to the disease. Thus Hemmes found that in 47 families each with an affected child this child was the first-born in 18 cases, while of 254 children other than the first-born in these families, 29 were affected. It thus appeared that first-born children were about thrice as liable to the development of retinoblastoma as those born later. It must be noted, however, that Hemmes's cases were all sporadic ones with no evidence of a family tendency. Should such a series happen to include one or more families with many affected siblings it is clear that there would then be a much less striking difference between first-born and later-born children than in Hemmes's series.

(5) Race incidence

In addition to reports of retinoblastoma affecting almost all European peoples the disease has also been seen in negroes (Cohen, Jaffe), Chinese (Hu Ch'in), and other oriental peoples. Jungherr and Wolf give several references to retinoblastomas in animals.

FAMILIAL AND HEREDITARY INCIDENCE

While many cases of retinoblastoma appear isolated or sporadic, no siblings or other relatives of the child being affected (Berrisford, and Hemmes) there are many striking instances of familial incidence and an inherited liability to the disease (Bell, Weller). One of the most remarkable of these was an Australian family recorded by Newton (1902), in this family 10 of 16 children died of retinal tumours, 7 having bilateral growths, and there was a history that the father's brother had died in infancy of an eye complaint. Another Australian family reported by Maher (1902) was notable not only because 3 of 4 children were affected, 2 with bilateral growths, but also because all 3 remained well several years after enucleation of their eyes.

The occurrence of retinoblastomas in members of two or more different generations of a family, indicative of a transmitted liability to the disease, is less

is not attained until the fourth month after birth. The epithelium of the ciliary body and of the posterior surface of the iris represents the lip of the optic cup and the extreme periphery of the inner layer of the cup, and the insensitive ciliary part of the retina retains a primitive columnar or partly transitional kind of epithelium which is demarcated from the sensitive retina by the ora serrata.

It is relevant to note here the discovery of experimental embryologists that pieces of embryonic retina are capable of almost perfect self differentiation when isolated from their normal connexions and transplanted to other parts of the

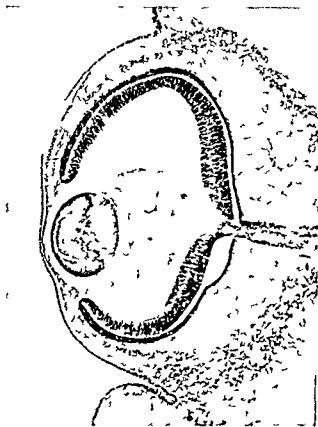


FIG. 435.—Section of optic cup and stalk of 28 mm. human embryo showing early stratification of retina proper and dense pigmentation of outer layer of cup ($\times 52$).

body (Lewis 1908) or cultivated *in vitro* (Strangeways and Fell 1926). This makes it less surprising that almost perfect differentiation of rosettes of rod and cone cells or even of stratified retina like layers should be seen under the abnormal anatomical conditions prevailing in masses of tumour tissue.

RETINOBLASTOMAS

HISTORICAL OUTLINE

In their advanced stage of fungation on the face the retinal tumours of infancy and childhood are so distinctive and horrible that their recognition as a clinical entity long preceded their pathological study. In the latter half of the eighteenth century they figured among the cases of *fungus haematodes* of the British

and orbital tissues were unaffected but both optic nerves were infiltrated and enlarged by growth as far back as the chiasma (Fig 442). The brain showed over its entire surface a continuous layer of soft white growth up to 4 millimetres thick which also clothed the surface of the spinal cord. Marked internal hydrocephalus was present with moderate enlargement of the skull and exaggerated convolutional markings on its inner surface. In the diploe of the temporal and parietal bones some of the main vessels were accompanied by ramifying white strands of growth. No tumour deposits were found in any other bones nor in any cervical thoracic or abdominal viscera. Microscopic examination showed the ocular tumours to be typical retinoblastomas consisting mainly of masses of rounded cells with plentiful areas of necrosis with some calcification but some areas of tumour showed well differentiated rosettes and fibrillated tissue (Figs 437-438). The tumour deposits in the optic nerves and on the surfaces of the brain and cord consisted of diffuse round celled growth devoid of rosettes and fibrils.



FIG 437—*Case II* Retinoblastoma showing areas of rosetted and fibrillar tumour ($\times 150$)

As Duncan and Maynard point out in their report, the slightly different course of the growth in the twins was largely attributable to surgical interference in Twin I, in whom trephining of one eye was followed by extension to the orbit and massive cervical metastases, with earlier death and less pronounced intracranial extension than in Twin II. Otherwise the 2 cases were strikingly alike in all respects.

Case III was a female child born of the same parents 16 months after the death of the second twin. When 10 months old this child who was under the care of Dr Mark Gardner had one eye excised on account of a large retinoblastoma which is depicted in Figs 436-439 and 440. This tumour was better differentiated than those in the twins containing many beautiful rosettes however mitotic figures were numerous. The retina was extensively detached but the growth was confined to the vitreal chamber and did not involve the optic nerve. Some months later examination disclosed a tumour in the other eye which however the parents refused to have removed. This grew steadily but was still confined to the eye when the patient was last seen at the age of 4 years.

commonly observed than its appearance in siblings. Weller has reviewed 30 recorded families in which such transmission occurred comprising 102 definite cases and 6 likely cases of the disease. In 14 families the father of retinoblastomatous children had had his eye removed for this disease in his childhood; in 7 families the mother had had retinoblastoma in childhood, and in 8 families the tendency was transmitted through non affected parents, in 4 instances through the father and in 4 through the mother, brother or sisters or other relatives of the parents having had retinal tumours in childhood. Weller gives a record of a family in which retinoblastomas may have occurred in four successive generations though there is no proof of the nature of the disease in the two early generations. Proven retinoblastomas occurred in a father and his two daughters and the father's father and grandfather were both said to have had their eyes removed in childhood. A striking example of transmission from a grandparent to grandchild through an unaffected mother is afforded by the family record given by Berrisford: the grandfather had had his eye removed in infancy in 1859 and his son had had his eye removed for retinoblastoma in 1898 at the age of 3 years and had died when 15 years old; the old man's daughter however escaped her brother's fate and remained unaffected but 4 of her 8 children developed retinoblastoma bilaterally in 3 cases and all 4 died at or before their fourth year.

The mode of transmission of the liability to retinoblastoma is uncertain. There is no clear indication of either Mendelian dominance or recessiveness. There is no sex linkage and as the families cited above show transmission takes place about equally through either male or female parents.

Although sporadic cases of retinoblastoma are more common than familial ones, from a genetic aspect the difference may be more apparent than real. As Weller points out the first case to be observed in a family will necessarily appear to be sporadic, but if this individual survives he or she may later propagate a retinoblastomatous family. Weller sums up the eugenic aspect of the subject as follows: "Sterilization of any child who survives enucleation or irradiation for retinoblastoma and the interdiction of further progeny to the parents of a child with retinoblastoma appear to be justifiable measures."

Twins with identical retinoblastomas have been recorded by Benedict (1929) and by Duncan and Maynard (1939). As I personally performed the necropsy and made the histological study of the tissues from one of the twins described by Duncan and Maynard and as a subsequent case of retinoblastoma occurred in the same family I give here a brief outline of the 3 cases which also illustrate other features of the disease.

Cases I and II were apparently identical female twins of Italian parents. During the twin pregnancy the mother had had severe anaemia from lead poisoning. At the age of 7 months both twins were found to have advanced bilateral retinal tumours. *Twin I* following a trephine opening of the right eye later showed extension of the growth into the right orbital tissues with subsequent orbital recurrence after enucleation of the eye as well as a large fungating mass in the right side of the neck and death occurred at the age of 19 months. *Necropsy (Dr Maynard)* showed also extension along the optic nerve scattered discrete deposits of growth on the base of the brain and involvement of the right apical pleura doubtless from the large mass of secondary growth in the right side of the neck. No secondary growths were found in any other thoracic or abdominal viscera. *Twin II* died 5 months later at the age of 24 months. *Necropsy (Willis)* showed extensive disorganization of the interior of both eyes by partly degenerated growths. The sclerae

enucleation of both eyes without recurrence in either the orbits or cranial cavity, thus Collins (1896) reported 4 cases of bilateral retinoblastoma cured by enucleation of both eyes, and I have already cited a similar experience of Maher s

MICROSCOPIC STRUCTURE

In many retinoblastomas the bulk of the tissue consists of cellular round celled growth devoid of any special cellular arrangement, showing plentiful mitotic figures, and prone to patchy necrosis. In areas of necrosis, mantles of surviving tumour cells often persist around blood vessels, and some calcification of the degenerated tissues is frequent.

Parts of the growth, however, may show structural differentiation in the form of rosettes or fibrillated areas or both. Usually these are present in parts only of an otherwise diffusely cellular tumour, as in Case II above, but some tumours show plentiful rosettes or fibrillation, as in Case III.

The rosettes of retinoblastomas, which were first observed by Flexner and have never been described better than by him, are depicted in Fig 439. Each rosette in section consists of a group of 15 to 40 or more elongated cells arranged radially around a central circular or oval cavity 10 to 60 microns or more in diameter. The nuclei of the cells occupy their outer or basal ends and lie in a rather even ring at the periphery of the rosette. The apical or centrally directed parts of the cells tend to taper towards the lumen, some of them lie in contact with each other, while some show fine slit like spaces between the tapering cells. Near its apical end each cell bears a fine but distinct transverse mark where it traverses the delicate but distinct membrane which demarcates the lumen of the rosette. The contents of this lumen may consist of distinct rod shaped or bulbous processes of the cells internal to the membrane, or of granular debris. As Flexner noticed, rosettes with distinct cell processes within the lumen contain little or no amorphous debris, and rosettes with plentiful debris show no distinct cell processes, and it is clear that the debris results from disintegration of the processes. The whole structure is unmistakably identical with that of the rod and cone layer and external limiting membrane of the normal retina, and even the contents of the lumen of the rosette resembles that of the sub retinal space of a detached retina in which rods and cones may still be distinct or may disintegrate to granular amorphous material. (Compare Fig 436 and Fig 439.)

The basal or nucleated ends of the rosette cells are crowded together and usually have indistinct outlines, but sometimes, as Flexner again noticed, a distinct fine fibrillary process may be seen to arise from the base of a cell and to penetrate amongst the surrounding tumour cells. The nuclei of the rosette cells are identical in appearance with those of the clustered unarranged tumour cells around. Each nucleus is spherical or ovoid, 7 to 10 microns in diameter and has a rather distinctive punctate chromatin pattern consisting of scattered fine particles accompanied by a few coarser particles, and no distinctly vesicular nucleolus. The unarranged tumour cells around and between the rosettes have scanty ill defined cytoplasm, the nuclei often appearing to be naked. Mitotic figures occur in both the unarranged cells and in those of the rosettes. Occasionally, as Flexner observed, a rosette is seen with its lumen occupied by one or two round tumour cells, evidently intruders from the proliferating tumour tissue around.

SITUATION MULTIPLE AND BILATERAL TUMOURS

Most of the tumours arise in the posterior parts of the retina, especially in its lower half. Even in early stages the ophthalmoscope often shows multiple foci of growth sometimes 'a plentiful sprinkling of the whole retina with miliary growths' (Duke Elder). While some of these may be due to metastatic seeding via the vitreous or via the sub-retinal space behind a detached retina it is clear that many of them are multiple independent primary foci, as in Case I.

Bilateral tumours are frequent, occurring in about 25 per cent of cases e.g. in 97 of 405 cases in Wintersteiner's series. Bilateral disease is much more frequent in familial and inherited cases than in sporadic ones, as is exemplified in Newton's, Maher's and Berrisford's cases already cited and in Cases I, II and III above.

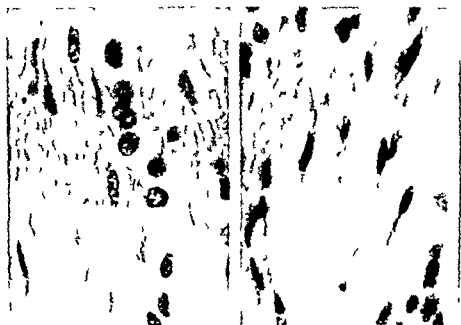


FIG. 438.—Case II. Detail of fibrillar area of Fig. 437 ($\times 800$).

The tumours may be discovered simultaneously or nearly simultaneously in both eyes and one or both growths may be present at birth. More often however there is an interval between the times of appearance of the tumours in the two eyes. The interval is usually only a few weeks or months, occasionally it extends to several years e.g. 11 years in Maghy's case. Bilateral growths are *not* due to spread from one eye to the other by way of the optic nerves but are independent primary growths. This is shown conclusively by the following facts: (1) Ophthalmoscopic examination shows that the tumours in the second eye arise in any part of the retina and do not necessarily or even usually appear at the optic disc. (2) The first affected eye has often been enucleated at an early stage when the growth is still purely intra-ocular and the optic nerve is microscopically free from growth. (3) When the second eye has been enucleated its nerve also has often been found uninvolved. (4) Patients with bilateral growths have survived

Fibrillated tissue is less common than rosettes, and indeed well marked fibrillary differentiation has seldom been mentioned at all in descriptions of the histology of retinoblastomas. Case II (Figs 437, 438), however, affords a good example of a tumour with areas of prominently fibrillated tissue. The cells, many of which are elongated, are separated by masses of fine wavy fibrils more or less parallel in direction. The nuclei are similar in appearance to those of the more cellular areas of the tumour. The cytoplasm is scanty and indistinct, but in places it can be clearly seen that the fibrils are processes of the cells. The fibrils stain rather faintly with the usual stains, and Van Gieson's, Mallory's and Masson's stains show that they are non collagenous. As my specimen was embedded in paraffin, it was unsuitable for applying special stains for neurofibrils or neuroglia, and I am not aware that this has ever been done convincingly with any tumour of this kind. However, from the obviously similar nature of the cells of the fibrillated areas and those of the more usual round celled growth in other parts of the same tumour, and from the fact that the fibrils are processes of these cells, it seems clear that in this tumour at least the fibrils are of true neural, not neuroglial, character, and that they correspond to those of the plexiform or fibre layers of the normal retina.

As long ago as 1904, Verhoeff observed that the supposedly round cells of retinal tumours are in fact often elongated, and in one tumour the cells resembled 'the bipolar cells of the adult retina, having a delicate process at each end. The processes were often quite long, stained only faintly and their endings could not be made out. The tumor contained rosettes in great numbers. In at least three other tumors the writer has been able to make out numbers of cells with such processes'. The cells described by Verhoeff were undoubtedly the same as those depicted in Fig 438, and I am satisfied that his identification of them as bipolar cells of the inner nuclear layer was correct.

Growths with well developed retina-like structures, like that depicted by Susman, would afford the best material in which to display conclusively the nature and relationships of the fibrils.

Do neuroglial cells and fibres ever differentiate in these tumours? There is no inherent improbability in such differentiation, but it has not been proved to occur. We have already noted Greeff's and Hertel's early claims to have demonstrated neuroglial 'spider cells' in retinal 'gliomas', and Leber's and Verhoeff's criticism of these claims. More recent workers who believe they have identified neuroglial elements in these tumours include Urra and Grinker, but their descriptions and illustrations are far from convincing. Neither of these writers displays any healthy doubts regarding the specificity of the silver impregnation method he has used, and neither gives any details of his technique, or any evidence that he has adequately controlled his results. Grinker's claim to have identified 'astrocytes', 'astroblasts', "spongioblasts" and "oligodendroglia" using an unspecified technique ("Kanzler" method according to one of the legends), will not satisfy many histopathologists, nor will Urra's highly diagrammatic drawings of all too-perfect 'astrocytes'. Neuroglial elements, both astrocytes and Muller's cells, may well occur as an accompanying stroma in the more highly differentiated retinoblastomas, just as Schwann cells occur in

Rarely a retinoblastoma shows retinal differentiation even greater than rosettes. Elongated or irregular spaces may appear, into which project well

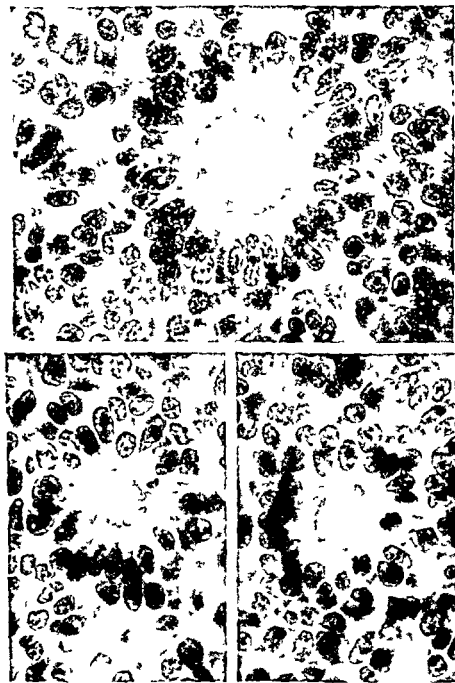


FIG. 439.—Case III. Retinoblastoma rosettes. Compare structure with that of Fig. 436. Note cells in mitosis in rosettes. (800)

differentiated rods and cones, and which are surrounded by nucleated and fibrillary layers exactly reproducing those of the normal retina. Susman has depicted an instance of this rare type of growth, unfortunately without recording any details

is unwarranted, so are attempts to homologize the variants of retinoblastoma with the different types of cerebral tumours. The derivation of the retina from the primitive neural tube is no valid reason for applying to retinal tumours our notions of the histogenesis of cerebral tumours. The retina is *not* the brain, and the retinoblastomas are *not* like any of the tumours of the brain. No sub division of the retinoblastomas is necessary, these tumours form a single histogenetic group the origin and nature of which are perfectly clear. As in other groups of tumours, there is a considerable range of structure and behaviour within

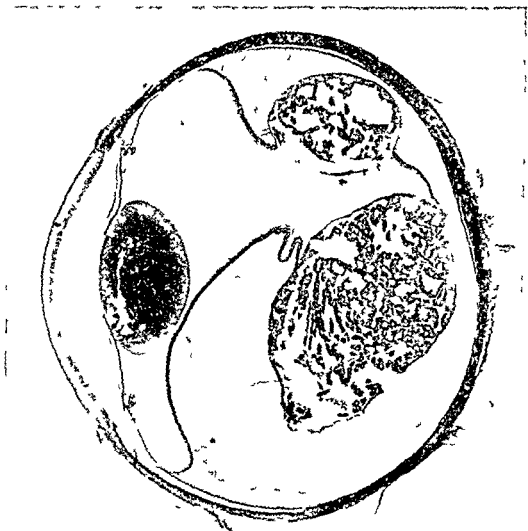


FIG 440—Case III Celloidin section of eye showing retinal detachment with retinoblastoma ($\times 5$)

the group, but this does not call for its sub division or for any elaboration of nomenclature

MODES OF SPREAD AND METASTASIS

(1) Intra-ocular extension

Forming first a nodule or plaque in the plane of the retina, a growing tumour may later project into the vitreous from the still attached retina, or more commonly

well differentiated ganglioneuromas but we still need proof of this by evidence much more substantial and precise than that so far advanced

HISTOGENESIS AND NOMENCLATURE

Comparison of the structure of the retinoblastomas and of the developing retina leaves no room for doubt as to the correctness of the view first advanced by Collins Ginsberg and Verhoeff and later crystallized in the name retinoblastoma, that these tumours are essentially embryonic, representing immature developing retinal tissue. Those which continue to proliferate at the embryonic level fail to attain any structural differentiation but when differentiation occurs it produces retina like structures most commonly rosettes of rod and cone cells less commonly fibrillary or plexiform retinal tissue and least commonly unmistakably retina like layers as in the case depicted by Susman. The identity of the constituents of a rosette with its typical elongated cells, its limiting membrane and its distinct rod like and cone like cell processes, cannot but be obvious to anyone who has examined a single good preparation of a retinoblastoma with well formed rosettes. Study of such a specimen will show how nonsensical is Fischer's suggestion that the embryonic tumours of the retina and the sympathetic system are essentially similar and should be classed together as neuroblastomas and Ewing's endorsement of this view in one place (on his p. 442) and his apparent rejection of it a few pages later (pp. 470-3) will seem pointless as well as inconsistent. If Fischer, Ewing and others had read and pondered Flexner's excellent original description of retinoblastomatous rosettes and had carefully examined one good specimen of them they could not have written such absurdities.

While Flexner and Wintersteiner correctly identified the rosettes as corresponding to the outer layers of the retina the implication in their writings and in those of others, that the rosettes represent superfluous foci of retinal cells (Cohnheim rests) from which the rest of the tumour tissue grows cannot be accepted. The rosettes are not the original source of the tumour but merely foci of retina like differentiation in the tumour tissue as it grows. The tissue of some retinoblastomas like that of some neuroblastomas matures to a greater or less degree as it grows. maturation of a neuroblastoma produces ganglioneuromatous structure maturation of a retinoblastoma produces retina like structure.

While it is clear that all parts of the immature retina may be represented in the tumours it seems probable that the most frequent and main source of the growths is the outer nuclear layer. Not only do the rosettes represent outer nuclear layer cells with their attached rods and cones but some early tumours have been seen to be continuous with the outer nuclear layer and to have the still intact inner layers of the retina clothing them on their inner aspect (see Duke-Elder's Figs. 2427 and 2447). On the other hand some early tumours clearly arise from the inner nuclear layer as in Ch. in's case and of course fibrillated areas with bipolar tumour cells represent this layer. However the precise zone of origin of the tumours is probably immaterial multiplying embryonic retinal cells probably all have equivalent potencies for differentiation.

Sub-division of the retinoblastomas into several types with corresponding elaboration of nomenclature as proposed by Grinker Favaloro and Susman

the lamina cribrosa and directly into the substance of the optic nerve which is enlarged and partially destroyed by tumour (Fig 442). Infiltration of the nerve may extend as far as the chiasma. In some cases extension takes place chiefly in the sheath around the nerve, and the cerebral sub arachnoid space is speedily invaded. Once the tumour has reached the cranial cavity, either *via* the nerve itself or its sheath rapid extension in the sub arachnoid spaces of the brain and cord ensues. This may be either in the form of discrete scattered metastatic deposits by way of the cerebrospinal fluid as in my Case I, or in the form of a more or less continuous sheet of growth over the surface of the brain and cord as in Case II (depicted by Duncan and Maynard), and in the cases of Hu,

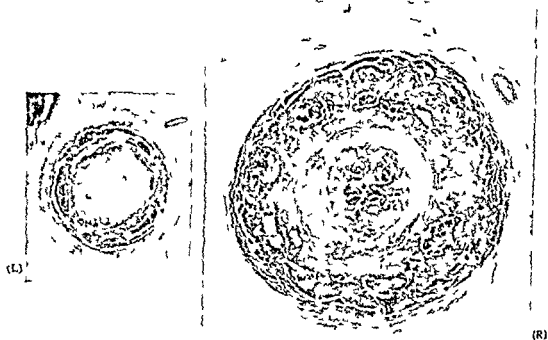


FIG 442—Case II Cross sections of optic nerves. The right nerve shows great distension of its sheath by growth and also a central mass of growth, the sheath of the left nerve is less distended and the nerve itself nearly intact ($\times 10$)

Cairns and Russell, and others. The dura mater and bones of the skull are not invaded from these intracranial growths, but there may be coexistent invasion of skull bones from the orbit, or metastases in them, or inconspicuous perivascular extensions into the diploe along the extra dural meningeal vessels, as in my Case II.

(ii) *Trans scleral extension to the orbit* takes place principally along the perivascular spaces of the vessels which perforate the sclera, the ciliary arteries and the venae vorticosae. The growth fills the orbital cavity, may cause proptosis of the eye, and appears on the face as a horrible fungating mass which may attain an enormous size. From the orbit direct invasion of the bones of the skull often ensues. Invasion of the cranial cavity from these does not occur, though of course there may be coexistent intracranial extension *via* the optic nerve.

(3) Metastasis

(i) *Metastasis by lymphatic channels* occurs only after extension of the growth to the orbit and face when metastatic growths may develop in the pre auricular

the retina suffers detachment and much of the growth comes to lie in the sub-retinal space (Fig 440) From the posterior half of the globe the tumour may spread forward to destroy the ciliary body and iris envelope the lens and invade the anterior chamber (Fig 441) Metastatic seeding may occur through either the sub-retinal space or the vitreous producing implants on other parts of the

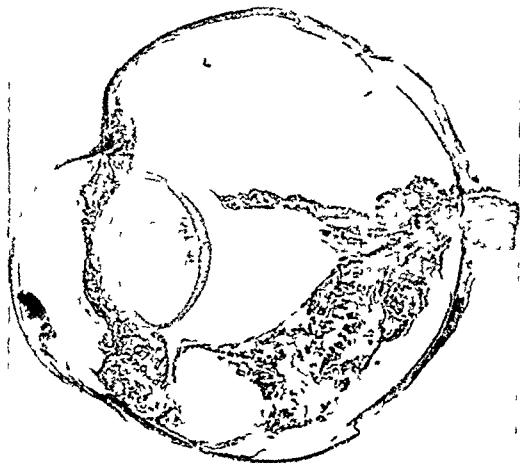


FIG 441 —Eye of an infant with retinoblastoma showing spread of growth to ciliary body and iris and over front of lens (5)

retina choroid ciliary body or iris Glaucoma degeneration and atrophy of the intra-ocular tissues ensue

(2) Extra-ocular extension

Extra-ocular extension of the growth takes place in two distinct ways (i) by the optic nerve and (ii) through the sclera to the orbital tissues

(i) *Extension by the optic nerve* is frequent and on its presence or absence post-operative prognosis largely depends Most deaths from retinoblastoma are due to intracranial extension by this route The growth infiltrates through

however, is shown by Gifford's report of a case of retinoblastoma in a child of $3\frac{1}{2}$ years, whose optic nerve after excision was found to be infiltrated right to its cut end, but who was well 20 years later, and by De Kleijn's report (cited by Gifford) of a similar case of a patient who remained well 61 years after enucleation.

The proportion of cures to be expected after enucleation is difficult to estimate with accuracy, but available figures (cited by Duke Elder) suggest that in operable cases, i.e. those with no clinically apparent extra ocular extension, more than 50 per cent can be cured by enucleation. The unfavourable results in the remainder depend almost entirely on infiltration of the optic nerves, microscopic examination of which therefore permits fairly accurate prognosis in most cases. Reese found that in 52 per cent of 119 eyes enucleated for retinoblastoma the growth had extended through the lamina cribrosa into the nerve, and in 43 per cent extension in the nerve reached right to its cut end thus rendering the prognosis next to hopeless.

Spontaneous retrogression of retinoblastoma is a rare but well authenticated event. Duke-Elder cites 11 cases in which spontaneous cure has been recorded and the after-history followed for many years, and the subject is also discussed by Hine and by Wells. In most of the cases, one eye has been removed because of a microscopically proven retinoblastoma, and then an ophthalmoscopically similar growth has appeared in the second eye and has retrogressed after attaining a certain size. In some cases the eye containing the retrogressed tumour has been atrophied and useless, in others a useful eye has remained. The ophthalmoscopic appearance of such a retrogressed tumour is distinctive (Duke Elder). In Knieper's case the right eye was removed at the age of $2\frac{1}{2}$ months and proved to contain a retinoblastoma, the left eye was also filled with growth, but the parents refused a second enucleation and the child was discharged. It was found 11 years later alive and well in an institute for the blind, with an atrophied left eye. In Stallard's case (cited by Duke Elder) retrogression followed a severe attack of scarlet fever, the patient subsequently had 2 children, both of whom had bilateral tumours. In the cases reported by Hine, a father of 5 sons had had his left eye excised for retinoblastoma at the age of 2, and he also had a healed lesion in his right eye. Of his 5 sons, one died when 6 months old the other 4 all developed retinal tumours, bilateral in 3 cases, and one of the children with bilateral tumours showed spontaneous retrogression of both of the growths. It need scarcely be said that spontaneous cure by total degeneration of a retinoblastoma is so infrequent that it cannot be seriously considered in assessing prognosis.

TRUE GLIOMAS (ASTROCYTOMAS) OF THE RETINA

True astrocytic gliomas of the retina, comparable with the astrocytomas of the brain, are very rare. Examples have been reported by Dejean (1934), McLean (1937), and Marks, Willis and Anderson (1939). My study of the tumour in the last cited case, that of a girl of 11 years who was known to have had a slowly enlarging nodule near the optic disc since the age of 6, showed the tumour to be a smoothly hemispherical mass 9 millimetres in maximal diameter, lying to one side of the optic disc, replacing the external layers of the retina and clothed on its inner surface by the intact nerve cell layer of the retina. It consisted of a

and cervical lymph glands as in Case II. From these the tumour may spread to the mediastinal and other lymph glands and blood-borne metastases elsewhere in the body may also be accompanied by deposits in the corresponding lymph glands.

(ii) *Metastasis by the blood stream* is infrequent many cases succumbing to the local disease or its intracranial extensions without showing remote dissemination. Blood borne metastases most frequently affect bones these metastases may be very numerous and widespread involving both the medullary and subperiosteal tissues (Roman, Hu, Ch'in). Metastases in thoracic and abdominal viscera are rare in Wintersteiner's large series of cases the liver contained growths in only 7 cases the kidneys in 2, ovaries 2 lungs 1 and spleen 1. Hepatic metastases were present also in Roman's Jaffe's and Ch'in's cases pulmonary metastases in Lauber's case and ovarian metastases in Jaffe's case and Ch'in's case also had deposits in the pancreas and the muscles of the thigh. Lawson mentioned a deposit in the deltoid muscle. The rarity of deposits in the lungs is particularly noteworthy.

The structure of metastatic growths as of all extra ocular extensions, is usually diffusely cellular and devoid of any recognizable arrangement or differentiation of the cells. Occasionally however, rosette formation may be observed as in a metastasis in the fibula in Roman's case.

PROGNOSIS

Post-operative prognosis depends largely on the condition of the optic nerve of the excised eye. This should always be examined microscopically if it is infiltrated by growth the outlook is bad particularly if the infiltration extends to the divided end of the nerve. If it is unaffected and orbital extension has not occurred the risk of recurrence is not great and prognosis will now depend largely on whether a new tumour develops in the remaining eye. As we have already seen such bilateral development is most to be feared in cases with a strong familial predisposition to retinoblastoma. Needless to say however regular and frequent ophthalmoscopic inspection of the remaining eye should be made in all cases over a follow up period of at least 2 or 3 years and should a new growth appear in this eye its prompt enucleation should be advised. If microscopic examination shows the nerve of the enucleated second eye also to be free from growth, then the prognosis remains quite favourable. We have already mentioned cases of survival following bilateral removal of the eyes such as those of Maher and Collins and there is little doubt that lives have been lost as a result of temporizing on the part of the surgeon or unwillingness on the part of parents to consent to removal of both eyes. The proposition that death is preferable to permanent blindness from infancy of course does not lie within the scope of pathological discussion.

The all importance for prognosis of the condition of the optic nerve of a retinoblastomatous eye has a bearing also on surgical technique clearly in removing such an eye as much as possible of the optic nerve should be removed intact along with it. Division of an invaded nerve beyond the limits of invasion may avoid recurrence while division through an invaded part of the nerve is almost certain to be followed by recurrence. That this may not follow invariably

reviewed the previous reports of Badal and Lagrange, and Emanuel of similar tumours, and he fully discussed the close kinship of these growths with the retinal "gliomas", concluding that in neither group are the tumours gliomas but that they both consist of embryonic retinal tissue with appropriate regional differences.

One of the most remarkable, as well as one of the most beautifully depicted, examples of diktyoma since Fuchs's review, is that described by Spicer and Greeves. This tumour occurred in a male infant who developed "seven clear, transparent bladders or cysts floating in the aqueous. They moved freely and rebounded from each other or from the walls of the anterior chamber just like toy balloons." These cysts had thin nearly transparent walls, the largest was about 3 millimetres in diameter, and two of them gave off lateral buds. The eye was removed and many more cysts were found between the iris and lens and in the vitreous. These had arisen from a solid growth of the ciliary body, which contained rosettes identical in appearance with those of a retinal "glioma". The walls of the detached cysts had a microscopic structure perfectly simulating that of the embryonic retina.

As both Verhoeff and Fuchs pointed out, diktyomas are undoubtedly closely related to retinoblastomas. They are to the *pars ciliaris retinae* what the retinoblastomas are to the *pars optica*. Fuchs noted that the *pars ciliaris* still consists of immature cells in the sixth month of foetal life, when the *pars optica* is well differentiated. He also cited an observation of Helfreich's (1875), who, in the eye of a child of 1½ with a retinal "glioma", saw also membranous structures in the ciliary region composed of embryonic cells like those seen in diktyomas. It is also significant that rosettes like those of retinoblastomas may occur in diktyomas as in the case of Spicer and Greeves already cited.

(3) Malignant ciliary epithelial tumours

These are rather variable in structure, but subdivision of the group as originally suggested by Fuchs, serves no useful purpose. These tumours occur chiefly in adults, especially in eyes which have suffered previous inflammatory and degenerative changes. Growth is usually slow, but eventually the eye may be filled and its coats infiltrated. Metastases have not been described. In addition to the cases reviewed and described by Fuchs, examples subsequently reported which illustrate the variety of these tumours include those of Greeves, Meller, Hine and Barrow and Stallard. Microscopically the tumours consist of cubical or columnar epithelial cells, pigmented or unpigmented, arranged in various papillary, tubular, convoluted or reticulated patterns. In many cases the cells resemble those of the ciliary epithelium, from which the tumours clearly take origin. Fuchs's case was remarkable in several respects, the partly pigmented growths were multiple, arising not only in an annular manner from the ciliary body but also from the pigment epithelium of the retina at several points, and the old inflamed eye contained also masses of metaplastic bone, which were infiltrated by the growths.

RARE RETINAL TUMOURS OF OTHER KINDS

There occur occasional intra ocular growths of retinal or ciliary origin which cannot be placed with certainty in any of the preceding groups. Thus Alling

tangle of asteroid and fusiform cells with abundant fibrillary processes, the asteroid cells varying greatly in size and often containing multiple nuclei. Van Gieson's stain showed collagenous tissue only around the few small blood vessels which entered the tumour. The tumour fibres all stained yellow. Two patches of granular calcification were present. This specimen resembled in many respects the tumour studied by McLean, from the macular region of a woman aged 23. In McLean's case however, the growth replaced the inner layers of the retina leaving the external limiting membrane and the rods and cones intact, and it consisted largely of fusiform neuroglial cells with long fibrillar processes.

Both the clinical progress and microscopic structure of these tumours show relatively benign characters. They have been slowly growing and highly differentiated, and they have not metastasized or recurred. However, the number of reported cases is so small that we cannot yet decide what range of structure and behaviour tumours of this kind may display.

To be distinguished from true retinal gliomas are occasional cases of massive tumour like gliosis of the retina resulting from long standing inflammatory or degenerative disease e.g. that described by Friedenwald. We must also distinguish from primary retinal tumours extensions into the optic disc from gliomas of the optic nerve.

EPITHELIAL TUMOURS OF THE CILIARY BODY AND IRIS

Tumours of the *pars ciliaris* and *pars iridica retinae* or of their embryonic precursors are exceedingly rare. In his classical paper on the subject in 1908 Fuchs divided these into benign and malignant types and the latter into two sub-groups according to whether the growths consisted of embryonic or adult ciliary tissue and this classification has remained a satisfactory one.

(1) The benign tumours of the ciliary epithelium

Often called 'adenomas', these consist of tiny well defined nodules often not more than 1 millimetre in diameter composed of cells resembling and clearly derived from those of the unpigmented layer of the ciliary epithelium and occurring in the eyes of middle aged or old people. They may be not true tumours but rather focal hyperplasias related to senile changes but they may also be related to the progressively growing tumours of the ciliary epithelium to be described presently. A typical specimen is that reported by Velhagen.

(2) *Diktyoma*

This is Fuchs's name for a distinctive group of ciliary tumours occurring in children and consisting of tissue resembling embryonic retina. The tumour usually grows slowly infiltrates the ciliary body spreads over the posterior surface of the iris and may invade the anterior chamber or massively fill the eye. Although the tumour is locally destructive metastases have not been observed and enucleation of the eye is curative.

The most valuable of the earlier reports is that of Verhoeff who fully described a ciliary tumour from a child aged 21. The tumour had pedunculated globular excrescences which resembled little optic vesicles. Verhoeff also

- Gifford H (1926) *Contribs to Ophth Sci* p 63
- Ginsberg S (1899) *Arch f Ophth* 48 (1) 92
- von Graefe A (1864) *Arch f Ophth* 10 (1), 216
- Greeff R (1896) *Dtsch med Wschr* p 327
- Greeves R A (1911) *Trans Ophth Soc U A*, 31 261
- Grinker R R (1931) *Arch Ophth* 5 920
- Hemmes G D (1931) *Klin Mbl Augenheilk* 86 331
- Hertel E (1897) *Klin Mbl Augenheilk* 35 323
- Hine M L (1920) *Trans Ophth Soc U A*, 40 146
- Hine M (1937) *Ibid* 57 173
- Hirschberg J (1881) *Arch f Ophth* 10 44
- Hu C H (1930) *Amer J Path* 6 27
- Jaffe M (1934) *Arch Ophth* 12 319
- Jungherr E and Wolf A (1939) *Amer J Cancer* 37 493
- KNIEPER, C (1911) Ein Fall von doppelseitigem Glioma retinae mit Enucleation des einen und nunmehr fast 11 jähriger Atrophie des andern Auges *Arch f Ophth*, 78 310
(Full discussion of cases of retrogression of retinal tumours)
- Lange H (1938) *Klin Mbl Augenheilk* 101 854
- Lauber (1907) *Klin Mbl Augenheilk* 45 270
- Lawson G (1885) *Trans Path Soc Lond* 36 418
- LEBER, T (1911) Beiträge zur Kenntnis der Struktur des Netzhautglioms, *Arch f Ophth*, 78 381 (An excellent cytological study)
- Lewis W H (1908) *Amer J Anat* 7 259
- Maghy C (1919) *Brit J Ophth* 3 337
- Maher W O (1902) *Austral Med Gaz* 21 413
- Marks E O Willis R A and Anderson J R (1939) *Trans Ophth Soc Australia* 1 46
- McLean J M (1937) *Arch Ophth* 18 255
- Meller J (1913) *Arch f Ophth* 85 191
- Newton R E (1902) *Austral Med Gaz* 21 236
- Orton R H and Willis R A (1944) *J Path Bact* 56 255
- Parker W R, and Stokes W H (1926) *J Amer Med Assoc* 87 1891
- Reese A B (1931) *Arch Ophth* 5 269
- Roman B (1912) *Beitr path Anat* 53 69
- Schuster H (1928) *Virchows Arch* 269 97
- SPICER, W T H, and GREEVES, R A (1914) 'Multiple cysts in the anterior chamber derived from a congenital cystic growth of the ciliary epithelium' *Proc Roy Soc Med* 8 (Ophth Sect) p 9 (An excellent report of an unusual case of diktyoma)
- Strangeways T S P and Fell H B (1926) *Proc Roy Soc Lond B* 99 340
- Susman W (1938) *Brit J Ophth* 22 722
- Urra (1923) *Arch f Ophth* 112 133
- Velhagen C (1917) *Klin Mbl Augenheilk* 58 239
- VERHOEFF, P H (1904) A rare tumor arising from the pars ciliaris retinae *Trans Amer Ophth Soc* 10 351 (An excellent account of a diktyoma and discussion of its relation to retinoblastoma)
- Verhoeff P H (1922) *Arch Ophth* 51 120
- WELLER, C V (1941) The inheritance of retinoblastoma and its relationship to practical eugenics, *Cancer Res* 1 517 (An excellent review of pedigrees showing inheritance)
- WELLS H G (1940) Occurrence and significance of congenital malignant neoplasms, *Arch Path* 30 535 (Includes a valuable discussion of retinoblastomas)
- WINTERSTEINER, H (1897) *Das Neuroepithelioma Retinae* Vienna (The classical monograph on the subject)

described a large ciliary growth in a boy 4 years old which consisted of a network of epithelial cells and islands of cartilage Knapp and Verhoeff were of the opinion that it differed from the epithelial tumours of the ciliary region and called it an 'endothelioma' on what grounds it is not clear The photographs suggest a diktyoma, and the presence of cartilage in such a tumour would be no more surprising than in an embryonic tumour of the kidney or liver

Schuster described a heavily pigmented tumour in the eye of a woman aged 32 with extension along the optic nerve, metastatic deposits on the surface of the cerebellum and in the spinal theca and with metastases also in the liver and many lymph glands Microscopic examination showed a pigmented epithelial growth with gland like orientation of its cells, the epithelial character of which was most evident in the metastases The tumour was interpreted probably correctly, as having arisen from the pigmented retinal epithelium If this was so, the tumour was then allied to the malignant ciliary tumours just described (see especially Fuchs's case) but was unique in having extended outside the globe and in having produced metastases

Orton and I have described a retinal tumour of peculiar structure from a woman aged 79 This nearly filled the vitreal cavity, and consisted of bands of elongated cells with their long axes transversely across the bands and with processes attached to the connective tissues on either side These characters led to the conclusion that the tumour had arisen from the radial fibres of Muller and was distinct from the astrocytic gliomas of the retina

REFERENCES

- Alling A N (1904) *Trans Amer Ophth Soc* 10 265
 Barrow R H B and Stallard H B (1932) *Brit J Ophth* 16 98
 BELL, Julia (1922) Glioma retinae *Treasury of Human Inheritance* Part I Sect VI London (A valuable collection of pedigrees of familial retinoblastomas)
 Benedict W L (1929) *Arch Ophth* 2 545
 BERRISFORD P D (1916) Statistical notes on glioma retinae with a report of 41 cases *Royal London Ophth Hosp Rep* 20 296 (A useful epitome of frequency age and sex incidence etc)
 Cairns H and Russell D (1931) *Brain* 54 377
 Chin K Y (1941) *Amer J Path* 17 813
 Cohen M (1930) *Arch Ophth* 4 368
 Collins E T (1896) *Researches* London
 Collins E T (1896) *Trans Ophth Soc U.K.* 16 142
 Dejean C (1934) *Arch d Ophth* 51 257
 DUKE-ELDER, W S (1940) *Text Book of Ophthalmology* Vol III pp 2449-2453 and 2812-2843 London (Valuable outlines of the several kinds of retinal tumours)
 Duncan W J and Maynard R B (1939) *Trans Ophth Soc Australia* 1 125
 Emanuel C. (1900) *Virchows Arch* 161 338
 Favaloro G (1938) *Monatsh Augenheilk* 100 577
 Fischer B (1918) *Zbl allgem Path* 29 545
 FLEISCHER S (1891) A peculiar glioma (neuroepithelioma?) of the retina *Johns Hopkins Hosp Bull* 2 115 (The first and best description and interpretation of the rosettes in retinal tumours)
 Friedenwald J S (1906) *Contribs to Ophth Sci* p 23
 FUCHS L. (1908) Wucherungen und Geschwulste des Ciliarepithels *Arch f Ophth* 68 534 (The classical paper on ciliary tumours)

depicted by Dawson, and was succinctly epitomized by Nicholson (1922) as follows

"A young mole is covered by epidermis, with highly irregular, elongated and branched papillae. The columnar basal cells, and to a lesser extent all those of the rete Malpighi are often deeply pigmented, especially in the deep parts of the papillae. The hair follicles, sebaceous and sweat glands, if present, participate in the changes. The basal cells have a marked tendency to become loosened and to pass into the corium, becoming detached from the epidermis. This is usually most clearly apparent at the apices of the papillae. But this loss of cohesion occurs within the substance of the papillae as well, nests of oval or round cells with relatively small, darkly stained nuclei and homogeneous "glassy" cytoplasm



FIG. 443.—Pigmented mole of arm of a girl aged 8 showing papillary structure, frayed epidermis and masses of naevus cells. (Deeper parts of dermis showed neurofibromatoid changes.) ($\times 40$)

resulting. These are the naevus cells. They are generally more or less deeply pigmented. They lie loosely side by side, and are no longer organically connected with each other by prickles. The nests of naevus cells are at first entirely intra-epithelial. Sooner or later, however, their epithelial covering gives way on the deep aspect of the papilla, and they are then partly surrounded by connective tissue. Fresh nests are constantly produced, and the old ones pass more and more deeply into the corium. They enter the tissue spaces of the corium and form irregular columns, which have usually lost their connections with the epidermis. Many of these loosened epidermal cells do not assume the characteristic form described, but are oval, flat or branched. Multinucleated giant cells are not uncommon. Depigmentation constantly takes place, the pigment being taken up and removed by leucocytes and the fixed cells of the corium, so that old quiescent moles often contain little or no pigment, except generally in the basal

CHAPTER 58

THE MELANOMATA

MELANOMA means only melanin pigmented tumour. Much of the confusion regarding the histogenesis of such tumours has arisen from supposing them all to be of similar origin—all mesodermal all epithelial or all neuroectodermal. Let us, at the outset abandon this assumption and consider separately the several groups of melanotic tumours according to their sites of origin. The principal of these in mammals are the skin the eye and the lepto-meninges. There is no reason to suppose that normal melanin production in these three main sites and in some subsidiary ones (e.g. certain nerve cells) is subserved by cells of similar nature or origin. The basal cells of the epidermis, the pigmented epithelium of the retina the dendritic pigment cells of the choroid and of the meninges, and the nerve cells of the substantia nigra, have no close affinity yet they are all melanin producers. Clearly then we should consider the melanomas of the various tissues separately from each other, and not force them artificially together in accordance with this or that hypothesis regarding the specificity of 'melanoblasts'. 'Melanoblasts' are not cells of a specific type but are of as many and diverse kinds as there are different tissues capable of producing melanin. Consequently, 'melanoblastomas' are not tumours all of one specific type, but show a corresponding diversity. Those who are interested in the attempts of Ribbert and others to interpret all melanomas as derived from specific "melanoblasts" (Ribbert called them 'chromatophores') will find them well set forth and critically examined in J. W. Dawson's classical monograph.

We will discuss melanomas under the following headings,

- 1 Melanomas of the skin
- 2 Melanomas of juxta-cutaneous mucous membranes
- 3 Intra ocular melanomas
- 4 Meningeal melanosis and melanomas
- 5 Melanomas of other tissues
- 6 Melanomas in animals
- 7 General conclusions

MELANOMAS OF THE SKIN

(1) The pigmented mole or naevus

The common pigmented mole or naevus is not a tumour but a malformation. But, since nearly all cutaneous melanomas arise in pre-existing moles the structure of these affords the essential clue to the histogenesis of the tumours. Pigmented moles are probably always congenital with rare exceptions they are discovered at birth or soon after. They show a definite life history comprising an early period of active development in childhood a stage of quiescence in early adult life and thereafter a stage of atrophy. Only in the first period in children is their mode of origin apparent. This was studied in great detail and beautifully

containing abundant clusters of small naevus cells mainly unpigmented quite detached from the epidermis and lying in thickened fibrotic dermis (Fig 446) The deeper parts

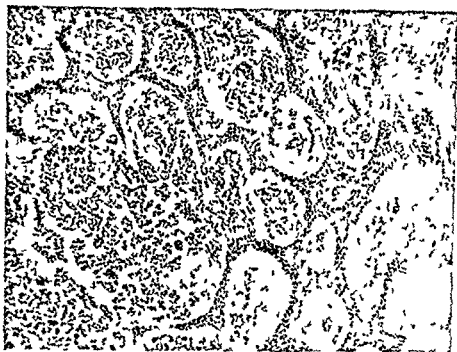


FIG 445 —Papillary pigmented mole of back of girl aged 18 showing clusters of naevus cells detached from epidermis ($\times 120$)



FIG 446 —Case I Detached clumps of naevus cells in dermal papillae and deeply pigmented epidermis ($\times 120$)

of the lesion consisted of whorls and bundles of cellular fibroblastic tissue similar to that of the benign lesions of neurofibromatosis and clearly related to the cutaneous nerves (Fig 447) In places there was an intimate admixture of neurofibromatoid whorls and

cells of their epithelial papillae. Moles often persist in this state for long periods of time. Sooner or later, however, the naevus cells disappear and the corium between the epidermal papillae then consists of a dense connective tissue.'

I cannot understand how any histopathologist who has examined young moles in their early formative stage can fail to endorse Dawson's and Nicholson's descriptions and to agree with their conclusion that naevus cells are detached epidermal cells. This seems to me to be too obvious for argument. The structure of young moles shows plainly that the naevus cells do *not* take origin from the sheaths of nerves or any other dermal elements but from the epidermis and the epidermis only.



FIG. 444.—Detail of Fig. 443 showing identity of frayed epidermal and naevus cells ($\times 120$).

To Nicholson's summary just cited I would add that some young moles show the development of naevus cells not as isolated nests in the epidermis but as a general loosening and detachment of the entire basal-cell layer. An example of this from a child aged 8 is depicted in Figs. 443 and 444 in which the identity of the very abundant naevus cells with frayed out epidermis is obvious. Examples of moles from older subjects after completion of genesis of the naevus cells and when these are now quite detached from the epidermis are depicted in Figs. 445–447. The history and structure of one of these are worthy of note.

Case 1—A woman aged 29 complained that since childhood she had had a small black mole of the skin of the mid-dorsal region. At first this had been flat but later it enlarged slowly and became raised above the surface until at the age of 20 it was as large as a sixpence still smooth and black. Thereafter it continued to enlarge but its colour became lighter. When excised it was a well-circumscribed raised brown plaque 2 centimetres in diameter with a corrugated surface. The patient had no signs of any other skin lesions or other physical abnormalities. *History*—The structure was mainly that of a typical moderately papillary benign pigmented mole clothed by pigmented epidermis and

are nerves and nerve endings, so that it is not surprising to find these involved in the anomalous field of tissue

(2) The epithelial histogenesis of melanomas of the skin

With few exceptions, cutaneous melanomas arise from pre-existing moles. While the structure of young pigmented moles shows plainly the epidermal origin of the naevus cells, that of early malignant melanomas shows equally plainly their origin from naevus cells and from the epidermis itself. That the tumours take origin from naevus cells is not questioned even by those who suppose these to be of non epithelial neural origin, all stages in the transformation of naevus cells to malignant melanoma cells are often demonstrable. But the naevus cells are not the only source of the tumours, as Dawson and Nicholson (1923) showed, there is clear evidence of progressive tumour genesis from the basal cells of the epidermis also. A mole becomes malignant by cancerous conversion of already formed naevus cells, and also in many cases by the simultaneous splitting off from the epidermis of new broods of neoplastic naevus cells. Nicholson depicted a striking example of this process and rightly insisted that the appearances cannot be explained away as due to secondary infiltration of the epidermis. The change is plainly in the epidermis itself, whence the melanomatous cells proceed to invade the dermis.

Those who doubt the epidermal origin of the cutaneous melanomas point out that these tumours show no signs of epidermal differentiation, i.e. prickle cells and cornification. To which the reply is (a) that the same might be said of most basal cell carcinomas of the skin, (b) that, just as pigment formation is much more active in the basal cells of the epidermis than in its spinous and more superficial cells, so in a tumour the assumption by the cells of predominant pigment formative functions may well be accompanied by loss of the capacity for orderly epidermoid differentiation, and (c) there *do* occur occasional tumours which are both melanotic and epidermic, namely pigmented basal cell and squamous cell carcinomas (Bonser). May not these pigmented basal cell and squamous cell growths be the very "missing links" between the ordinary skin carcinomas on the one hand and the melanomas proper on the other? The fact that such tumours behave more like skin carcinomas than like melanomas is not very surprising. And surely the very existence of pigmented epidermoid growths of this kind points to the epithelial non neural origin of integumentary melanin and *ipso facto* of integumentary melanotic tumours.

It remains to add here certain other relevant facts. Bloch's "dopa" reaction a test for the presence of an intra cellular melanogen oxydase (well summarized by Spencer, Dawson, Laird, and Dawson *et al*) is given in common by the basal cells of the epidermis, those of hair follicles naevus cells and malignant melanoma cells. In foetal and infant skin visible melanin appears first of all in the basal cells of the epidermis, and Bloch's test shows that prior to the development of visible pigment these cells and these cells only, are "dopa" positive. These facts accord with the purely epithelial origin of skin melanin and of skin tumours producing melanin.

naevus-cell clumps but the two kinds of cells could everywhere be distinguished easily and there were no transitions between them

✓ This case introduces us to the association first noticed by Soldan and later stressed by Masson of pigmented moles with local neurofibromatoid changes. When searched for, distinct though often slight signs of dermal neurofibromatoid change can be found in a large proportion—perhaps the majority—of raised pigmented moles, and abundant nerve fibrils have been shown to traverse this tissue and to come into close relationship to the naevus-cell clumps. (It is necessary to add that some writers have certainly over-estimated the number of nerve fibres present and their intimacy with the naevus cells. The silver impregnation methods used are not as specific as is often supposed and impregnated collagen and reticulin fibres have undoubtedly been misidentified as nerve fibres.)



FIG 447—Case 1. Neurofibromatoid tissue adjacent to a deep sebaceous gland (120)

I find most of Masson's and Foot's figures unconvincing in this respect—indeed I think many of them show plainly that the supposed nerve fibres were connective tissue fibres.)

We will return presently to discussion of the neural relationships of pigmented moles and tumours. But I must anticipate this here by stating that in my view, when abnormalities of nerves are found in a mole these are merely a part of the malformation. The developmental disturbance producing a mole affects all of the constituent tissues in the disturbed field of skin. In addition to the hyperpigmentation, exaggerated papillation, naevus-cell formation and associated neurofibromatoid changes which we have considered, moles may show also great increase in the number and size of hairs and hair follicles, or increase of blood vessels giving angiomatous characters. I agree with Dawson, Innes and Harvey that the pigmented mole is a complex malformation—a manifestation of disturbed development of all ingredients of the skin. Amongst these ingredients

constituted about 4 per cent of skin and lip cancers. I encountered 9 cases of cutaneous melanoma in approximately 1,200 cancer necropsies.

(b) *Age and sex*

Melanomas occur at all ages, about three quarters of them develop between the ages of 30 and 70, but without special prominence in any particular decade (Affleck, Webster *et al*). They are rare in young children. Of peculiar interest are cases, like that reported by Weber *et al*, in which disseminated melanoma is transferred from mother to infant *in utero*. Males and females are about equally liable to melanoma.

(c) *Site*

No region is exempt, but the commonest sites are the head and neck, trunk and genitalia, and the feet. Except for the feet, the least frequent sites are the limbs, especially the hands (Peller, Webster *et al*).

(d) *Race*

It has often been stated that dark-skinned races are relatively exempt from melanoma, but I can find no sound evidence for this impression. The disease has often been observed in Negroes (Bishop, Webster *et al*), and Hewer reported 47 cases in Sudanese, in whom melanomas of the feet are relatively common.

(e) *Pre existing moles*

These are recorded in the majority of cases, e.g. in 65 per cent in the series of Webster *et al* and 84 per cent of Affleck's series. Since, in some cases small moles have certainly been forgotten or overlooked, the actual proportion of melanomas preceded by moles must be even higher than this.

(f) *Injury*

Caution is always needed in attributing a causative roll to injury in the genesis of tumours, but there are good grounds for believing injury to play a definite part in the causation of melanomas. These grounds are as follows:

- (i) In cases of melanoma supervening on a mole there is often a history of mechanical injury or of incomplete surgical removal, e.g. in 36 of 68 cases recorded by Webster *et al*. Of course, it is often not possible to be sure that the supposed irritation or attempted removal of the mole was not the result rather than the cause of the supervention of malignant change.
- (ii) In a considerable proportion of cases of melanoma of the foot or leg, there is no history of previous mole, but on the contrary a history suggestive of injury. Of Hewer's 47 melanomas in Sudanese 60 per cent were on the feet and a further 15 per cent on the legs, and Hewer suggested trauma as causative. Sub ungual melanomas are often not preceded by recognized moles, and the suggestion that trauma can be causative is at least plausible. I have seen a fatal melanoma arising without a pre-existing mole on the toe of a tile worker whose occupation involved long

(3) Objections to the hypothesis of neural origin of moles and melanomas of the skin

- (a) The main objection is that these lesions are as already insisted plainly of epidermal origin
- (b) The resemblance of some groups of melanoma cells to groups of Merkel Ranvier cells or Wagner Meissner corpuscles does not justify far reaching histogenetic conclusions. The shapes and mode of arrangement of the cells of malignant melanomas are very diverse and simulation of cell aggregates of many kinds can be found in them.
- (c) Too much has been made of the association of pigmented moles with neurofibromatoid changes and of the hyperneuria of some moles. As already stated I look upon these as merely part of the malformation, and whatever the relationship between the abnormal epithelial and neural tissues in the malformed area it still remains true that the pigmentation is in the former and not in the latter. It is quite possible that the formation of a pigmented mole may depend primarily on a disturbance of innervation that it may be primarily an area of malformed sensory end organs but if so its excessive pigmentation and the pigmented tumour which may spring from it are still epithelial in origin.
- (d) Normal neural sheath cells and sensory end organs are unpigmented and tumours known to arise from them—neurilemmomas and neurofibromas—are unpigmented. If cutaneous melanomas were of neural sheath origin it is strange that they should be the only lesions in which cells of this lineage acquire pigment formative functions.
- (e) Feyrter recognizing the objections to the hypothesis that Schwann cells are the source of naevus cells supposes these to come from certain special neuro-endothelial cells which are situated in nerve sheaths and which extend (as Masson's clear cells Kromayer's vesicular cells or Langerhan's cells) into the epidermis and he proposes to call them neuro-endotheliomas. This alas answers none of the foregoing objections.

There is of course one sense in which the neural hypothesis is compatible with the epidermal origin of naevi and melanomas. In so far as the epidermis is itself a sensory end organ its cells are neural. Free nerve terminals ramify in the epidermis and it is believed that the cells of Merkel Ranvier are themselves modified epidermal cells. Is it possible that the dermal sensory corpuscles also may contain epidermal cells split off from the epidermis during development? Is the splitting off and isolation of naevus cells an exaggeration of a normal process in the development of the sensory apparatus of the skin?

(4) Incidence and causation of melanomas of the skin

(a) Frequency

Fortunately melanoma is a relatively rare disease. Most people have one or more pigmented moles and only an infinitesimal fraction of the total number of these will produce melanomas. However since almost all melanomas do arise in moles removal of these especially when they are of such a size or site that they are liable to injury is a wise precaution. Peller estimated that melanomas

metastatic spheroidal-celled carcinoma The patient then volunteered the information that a small brown mole had been excised from the same site 2 years previously

Stout has reviewed examples of what appears to be intra epidermal amelanotic melanoma

(6) The spread and metastasis of cutaneous melanoma

The behaviour of no other tumour is so unpredictable as that of melanoma. A 'mole' unsuspected of malignancy or so small as to be overlooked may produce widespread rapidly fatal metastases. Or a 'mole' may have been removed and all but forgotten 5 or 10 or more years before disseminated melanomatosis develops. Or, rarely, a frankly malignant growth for which a bad prognosis is given is unexpectedly cured by excision. Or, more rarely still, a melanoma which has already metastasized undergoes spontaneous retrogression.

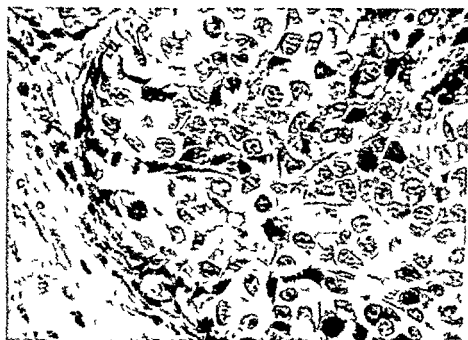


FIG 449—Amelanotic part of recurrent melanoma of calf of leg which recurred 4 years after apparently successful radium treatment of initial growth. Note mitotic figures ($\times 400$)

For examples of these and other anomalies of behaviour, see my 1934 work, and the papers of Wilbur and Hartman, Selig, Temple, and Webster *et al*. Fig 449 depicts a tumour which exhibited long delayed local recurrence.

The mode of dissemination of a particular tumour is equally unpredictable. Some tumours spread to surrounding parts *via* lymphatics and produce satellite tumours in the immediate neighbourhood or along the course of the main lymphatics. Others, while showing little spread locally, produce early metastases in the regional lymph glands (Fig 450). Others fail to metastasize by lymphatic routes but disseminate solely by the blood-stream. Blood borne metastases may develop in every organ and tissue of the body, or in one or two sites only, or there may be widespread dissemination yet with anomalous exemption of one or more main organs such as the liver or brain. Cerebral metastases or intestinal metastases

standing on a hot floor I have also seen a melanoma which had arisen without evidence of a previous mole at the margin of a chronic varicose ulcer

- (iii) The development of melanomas in mice and dogs following prolonged tarring is referred to in Chapter 4

(5) The structure of melanomas of the skin

Dawson's beautifully illustrated work renders it unnecessary to repeat in detail the histopathology of these growths. It must suffice here to state that their structure is very diverse—that their cells may be spherical polyhedral, fusiform or pleomorphic—that they may be arranged in epithelium like clumps, or in prominent perivascular mantles, or quite diffusely—that they may

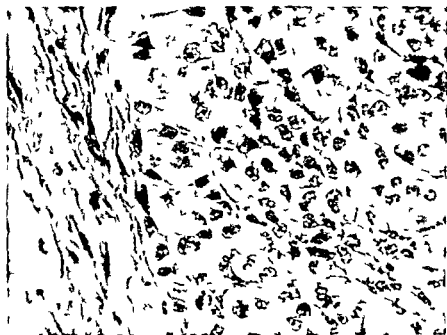


FIG. 448—Case II Amelanotic melanoma (400)

be deeply pigmented or unpigmented or may show pigmented and unpigmented cells in close contiguity—and that a single tumour sometimes shows many or all of these structural variants (See Figs 448–451)

Great experience is necessary in the microscopical diagnosis of early malignant change in pigmented moles. Suspicious features are increase in the size of the nuclei and cytoplasm of the naevus-cells, cellular pleomorphism, mitotic figures, the invasion of the overlying epidermis by groups of atypical cells and unequal distribution of intra-cellular pigment in different parts of the suspicious areas.

Amelanotic melanoma can cause great diagnostic difficulty as in the following case

Case II—1 or 9 months a man aged 36 had noticed an enlarging subcutaneous tumour of his calf. This was excised—it was a fairly well-defined white growth 3 centime res in diameter lying in the dermis and subcutaneous tissue—the epidermis was unaffected. Microscopically it presented the appearance shown in Fig. 448 and was diagnosed as

(7) A note on "blue naevi"

The Jadassohn Tische 'blue naevus', well described by Montgomery and Kahler, must be distinguished both clinically and histologically from the ordinary pigmented moles and melanomas. It is almost always congenital, it is situated most frequently on the face, forearms or hands, and less frequently on the trunk or lower limbs, it appears as a well circumscribed circular or oval, firm, blue or bluish black papule, usually only a few millimetres in diameter, it usually remains unchanged for life, except for gradual fibrosis with age in some cases, and the risk of supervening tumour is negligible. Microscopically, long fusiform, strap-like or branched melanin laden cells are found scattered diffusely or in irregular masses in the deeper parts of the dermis. According to Montgomery and Kahler, these cells show no special relationship to nerves. The more superficial parts of the dermis and the epidermis are normal, and the little malformation appears to be quite distinct from the ordinary pigmented mole, though the two occasionally coexist. The nature of the pigmented cells is undetermined, most workers suppose them to be mesenchymal. They are "dopa" positive, and appear to be identical with the so called "Mongol cells", which occur in the dermis over the sacrum and back and which are regarded as mesenchymal melanoblasts (Laidlaw). Montgomery and Kahler distinguish between "blue naevus" and 'Mongolian spot', the latter usually a poorly defined brownish area in the skin over the sacrum, present at birth and tending to disappear later, but microscopically the two are somewhat similar.

MELANOMAS OF JUXTA CUTANEOUS MUCOUS MEMBRANES

Primary melanomas are reported occasionally from the nasal cavity, mouth (New and Hausel, Gotschalk *et al*), conjunctiva or episcleral tissues (Dawson Duke Elder), rectum, and vagina or cervix (Taylor and Tuttle, Bromberg and Brzezinski). Needless to say, care must be exercised not to mistake secondary for primary growths in these and other unusual situations but there is no doubt that primary melanomas can arise in the juxta cutaneous mucous membranes. In most cases the histogenesis of these tumours is almost certainly the same as those of the cutaneous ones, i.e. from melanoblastic epithelium like that of the epidermis. In some cases this epithelium may actually be developmentally heterotopic epidermis, for we know that hairy 'naevi' can occur in the conjunctiva and in the oral mucosa. But we need not always postulate a developmental heterotopia, for epidermal structures can be acquired by metaplasia, in the vagina and cervix uteri at least. Thus Nicholson (1918 and 1936) has described the development of sebaceous glands, hairs and a pigmented mole in this situation, and I also (1936) have recorded the metaplastic formation of hairs in an endocervical polypus. It is quite probable, too, that the juxta cutaneous epithelia normally possess pigment formative capacities in slight degree witness their pigmentation in Addison's disease, etc.

Many mammals, of course show heavy pigmentation of their oral mucosae, e.g. different breeds of dogs vary greatly in this respect.

It is certain that the epibulbar melanomas are not always of conjunctival epithelial origin for epibulbar pigmentation clearly similar to meningeal pigmentation and unrelated to the conjunctival epithelium, certainly occurs



FIG 450—Metastatic round-celled melanoma in inguinal lymph glands a mass 4 centimetres in diameter which appeared a year after amputation of toe with a blood blister in a woman aged 60. Note groups of heavily pigmented and unpigmented tumour cells side by side ($\times 150$)

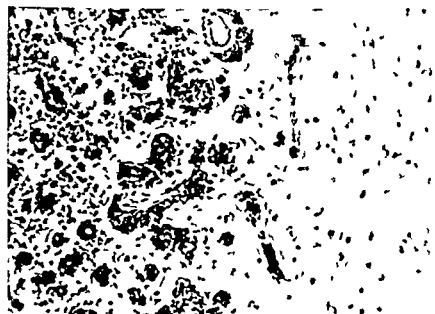


FIG 451—Metastatic melanoma of brain (Case XVIII of Trinea and Willis) showing perivascular spaces infiltrated by heavily pigmented cells ($\times 150$)

from unsuspected primary growths have caused many diagnostic errors (Willis 1934 Trinea and Willis 1936 and Fig 451). Metastases often develop in unusual sites e.g. mucous membranes endocardium testis or placenta

it is true that in structure and behaviour the ocular melanomas show general resemblances to the cutaneous ones, we must not ignore their differences. Spindle celled structure is much more prominent in the ocular tumours, which also show decided differences from the cutaneous ones in their metastatic propensities. Ocular melanoma produces remarkably frequent and often long delayed metastases in the liver, and it seldom effects widespread dissemination in almost every tissue of the body, as cutaneous melanoma often does. These differences should warn against over-zeal in attempting to formulate a common histogenesis for the ocular and cutaneous tumours. And, after all, the skin is not the retina and choroid and the pigmented tumours of the two may be comparable in nothing save their pigmentation.

(2) Incidence and causation

Intra ocular melanomas, which are relatively rare tumours, occur about equally in the two sexes. Children are rarely victims. Terry and Johns found the highest numbers of cases in the fifth and sixth decades, and Duke Elder estimated the mean age to be 50. The tumours arise in any part of the choroid, ciliary body or iris and are most frequent in the posterior half of the globe. Save that some of them appear to arise from pre-existing benign pigment spots in the choroid, nothing is known of their causation. An hereditary predisposition is sometimes suggested, but acceptable instances are exceedingly rare (Duke-Elder). The evidence that previous injury or inflammatory disease predisposes to melanomas is inconclusive. They are often unsuspected and undiagnosed, e.g. in 42 of the 94 cases reported by Terry and Johns.

(3) Structure

Little need be said of this. Diffuse or fascicular spindle celled structure is the commonest, rounded or polyhedral celled epithelioid structure is less frequent, and combinations and transitions between the two are often to be found. Most of the tumours are heavily pigmented, some of them so heavily that all cell details are hidden by the pigment. The degree of pigmentation often differs in different parts of the growths, especially in metastases, but complete absence of pigment is rare.

(4) Spread and metastasis

Extra bulbar extension is most often trans scleral, around the perforating vessels, and less often *via* the optic nerve. A greater risk, however, is metastasis by the blood stream. This often takes place from small tumours still confined within the globe and in some cases unsuspected.

Metastases may develop in any organ, and may not make their appearance for years after apparently successful removal of the eye. Prognosis is thus very uncertain. Mori recorded the development of widespread metastases 15 years after removal of the eye, Cairns saw orbital recurrence and a large metastasis in the scapula 16 years after enucleation of the eye, the interval between enucleation and the appearance of metastases was 18 years also in a case reported by Webb Johnson and McElleod, in H. G. W. Dawson's case subcutaneous and ovarian metastases appeared 14 years after removal of the eye, and Elsberg recorded spinal metastases

(see Case III below) and some epibulbar tumours arise far back on the sclera and well away from the conjunctiva

INTRA OCULAR MELANOMAS

(For a good general account of the incidence, structure and behaviour of these see Duke Elder)

(1) Histogenesis

In my opinion, the histogenesis of the melanomas of the uveal tract is still unsettled. There are three hypotheses as follows

(a) *The hypothesis of epithelial origin*

In favour of this hypothesis are the facts that in the embryonic eye melanin develops in the pigment-epithelium of the retina long before it appears in the choroid that the retinal epithelial cells are the only ones in the eye to give a positive dopa reaction at any stage of development, that there are substantial grounds for believing some malignant melanomas to arise from pre-existing benign choroidal pigment spots or 'moles' that the structure of these 'moles' is compatible with the idea that their cells may be split-off retinal epithelial cells analogous with naevus cells in the skin and that there is a general similarity of structure between the intra-ocular melanomas and the cutaneous ones. Some upholders of the epithelial view have supposed that the cells of the choroid are mesenchymal but receive their pigment from the retina. Others however, like Dawson believe that the dendritic pigment-cells of the choroid may be, not merely chromatophores which have received pigment from the retinal epithelium, but actually migrated cells of that epithelium.

(b) *The hypothesis of mesenchymal origin*

This is supported by the homology of the choroid and leptomeninges by the close resemblances to each other of the branched pigmented cells of these two membranes by the absence of histological evidence that the choroidal pigment is transferred from the retina or that the choroidal cells are derived from the retinal epithelium but that on the contrary they appear to be *ab initio* choroidal cells which develop pigment independently of the retina (Mann)

(c) *Masson's hypothesis of nerve sheath origin*

Masson's hypothesis was introduced in reference to the cutaneous melanomas only and even assuming that it were true for the skin tumours its extension (by Duke Elder and many others) to embrace the intra ocular growths is well appears to me to be unwarranted. As far as we know the choroid contains no sensory end-organs at all corresponding to the Merkel Ransier cells or Meissner corpuscles to which in Masson's view the cutaneous melanomas are related.

I find myself unable to decide between hypotheses (a) and (b). Further work is needed on the embryological histology of the eye more must be learnt of the structure and mode of origin of the benign naevi or moles of the uveal tract from which it seems clear some melanomas arise (Collins Hower Johnston Albers) and of early melanomatous changes in previously normal eyes. While

both the brain and dura mater and invading the superior longitudinal sinus. A few small brown or black spots were present on neighbouring parts of the cerebral surface. The pia mater of the base of the brain, especially the frontal lobes, showed extensive patches of grey pigmentation. The rest of the brain and its coverings were normal. Patches of slight brown pigmentation were present in the skin of the right side of the face and temporal area. The whole of the outer surface of the sclera of the right eye showed prominent brown patches and there was slight similar pigmentation of the left sclera. The intra ocular structures appeared normal. Except for pneumonia and multiple benign uterine myomas all the viscera were normal and careful search failed to disclose a primary melanoma or a scar of the skin. *Histology*—The tumour consisted of diffusely arranged heavily pigmented fusiform and rounded cells which invaded the dura mater and brain tissue (Fig 453). The pigmented patches in the pia mater contained many elongated pigment-cells resembling those of Fig 452 and the episcleral pigment patches showed similar cells.



FIG 453—Case III. M = main mass of growth on brain surface. B = brain with heavily pigmented tumour infiltrating perivascular spaces ($\times 60$).

This case is of special interest in showing not only an undoubtedly primary malignant melanoma of the meninges, but also associated melanosis of the meninges and (presumably) non epithelial melanosis of the epibulbar tissues and possibly of the skin also on the same side. Ordinary naevi of the skin were not present, but in some other cases extensive melanosis or melanomatosis of the meninges has been associated with multiple or widespread pigmented moles of the skin also (Grahl, Schopper, Lua, MacLachlan, Berblinger, Heilmann, Bjorneboe).

It is a notable fact that in none of the cases of indubitably primary melanotic tumours of the central nervous system have visceral metastases been found. In this respect the behaviour of meningeal melanomas differs strikingly from that of cutaneous and ocular ones, a difference which favours the view that they differ histogenetically. When, as in cases described by Hassin and Bassoe and by Foot and Zeek, supposedly primary melanomas of the brain or meninges have been

after an interval of 14 years Wilbur and Hartman reported 3 cases, each with metastases in the liver and subcutaneous tissues which appeared after intervals of 13 10 and 10 years respectively following removal of the eye These writers referred also to other examples of long delayed metastasis the longest interval being 32 years in Wilder's case



FIG. 452.—Normal meningeal pigment cells in a cleared lightly haematoxylin stained strip of pia mater from a Chinese male aged 37 ($\times 100$)

The liver is the favourite site of metastasis and may attain a huge size Rolleston found the average weight of the liver in 22 collected cases of ocular melanoma with hepatic metastases to be 6 000 grammes Hamburger recorded a liver weight of 10 000 grammes and I one of 7 850 grammes (1934 Case 117)

MENINGEAL MELANOSIS AND MELANOMAS

Elongated and branched pigment-cells are normally present in the pia mater especially of the base of the brain stem and especially in the dark skinned and Mongolian peoples (Fig. 452) The origin of these cells developmentally is uncertain the view often expressed (hoping to unify histogenetic concepts of all groups of melanomas) that they are of neuro-epithelial origin is only supposition they may equally well be mesenchymal They are certainly the source of diffuse melanosis and primary diffuse or focal melanotic tumours of the meninges and central nervous system Acceptable cases of this kind include those of Virchow (1859) Minelli Hirschberg Boit Kawashima Schopper Lur Kiel Omodei Zorini Kraft Dieckmann Heilmann Björnehoe and Akelutis and the following is an additional example

Case III Autopsy on a woman aged 46 who had had recent signs of cerebral tumour disclosed the following abnormalities. At the upper medial border of the right cerebral hemisphere there lay an irregular black tumour 4 centimetres in diameter consisting

of melanotic tumours The origin of the pigment cells of the meninges, from which primary meningeal melanomas arise, is undetermined, there is no evidence that they are derived from neuro epithelium or that they are not mesenchymal, and the meningeal tumours behave differently from cutaneous and ocular ones The histogenesis of the choroidal pigment cells and of the intra ocular melanotic tumours is still unsettled, it is possible that they may be derived from the pigmented layer of the retina, or from the mesenchyme of the choroid which is the homologue of the meninges, or from either Some epibulbar melanomas almost certainly arise from non epithelial episcleral pigment cells comparable with those of the meninges, but conjunctival epithelial naevus cell melanomas also occur

I conclude, as I began, by saying that I think it a mistake to regard all melanotic tumours as comparable and to try to devise a unified histogenetic hypothesis to embrace them all Their several tissues of origin differ greatly in development and function, and the corresponding several groups of tumours differ significantly from one another in structure and behaviour It may be contended that the essential community of all pigmented tissues is shown by cases (such as my Case III, and those of Berblinger, Bjorneboe, and others) in which developmentally abnormal pigmentation affects skin, eyes and meninges simultaneously This argument, strong though it appears to be, is not necessarily valid If melanin production is merely a common function of several distinct kinds of tissues, then factors disturbing that function might well do so simultaneously in those several tissues—just as diabetes may cause visible disturbances of glycogen or lipid metabolism in several distinct kinds of cells

It is not impossible that further research may lead to some unification of our concepts of melanin formation and of the histogenetic relationships of melanotic cells and their tumours At present, however, our knowledge is too incomplete to allow us to frame any unified hypothesis, and attempts to do so are forced and speculative

REFERENCES

- Affleck D H (1936) *Amer J Cancer* 27 120
 Akelaitis A J E (1935) *Amer J Path* 11 591
 Albers E S (1940) *Amer J Ophth* 23 779
 Berblinger W (1915) *Virchows Arch* 210 328
 Bishop E L (1932) *Amer J Cancer* 16 522
 Bjorneboe M (1934) *Frankfurt Z Path* 47 363
 Boit H (1907) *Frankfurt Z Path* 1, 248
 Bonser G M (1946) *Brit J Radiol* 19 229
 Bromberg Y M and Brzezinski A (1944) *J Obst Gyn* 51 147
 Cairns F D (1922) *Brit J Surg* 10 290
 COLLINS, E T (1926) Intra ocular melanomata *Trans Ophth Soc U K*, 46 86
 Davidsohn C (1909) *Verh Dtsch path Ges* 13 287
 Dawson E K Innes J R M and Harvey W F (1939) *Edinb Med J* 46 695
 Dawson E K (1946) *Brit J Radiol* 19 219
 Dawson H G W (1922) *Brit Med J* ii 757
 DAWSON, J W (1925) *The Melanomata their Morphology and Histogenesis* Edinburgh (Reprinted from *Edinb Med J* Oct 1925) (An indispensable classic)
 Dieckmann H (1930) *Virchows Arch*, 275 785
 DUKE-ELDER W S (1940) *Text book of Ophthalmology* Vol III pp 2471-2516 London (A useful well illustrated account of the ocular melanomas)

accompanied by metastases in other parts there is room for strong suspicion that a small primary growth of the skin or eye has eluded discovery or that (as in a case reported by Trinca and myself) a small skin lesion has been removed months or years previously and forgotten

MELANOMAS OF OTHER TISSUES

In my opinion the concluding sentence of the last paragraph applies also to most perhaps all, of the supposedly primary melanotic tumours of other viscera e.g. those of the adrenals reported by Davidsohn Schmidt Goldzieher MacLachlan and Smith and that of the gall bladder reported by Rosenthal. In such cases unless meticulous search of every part of the skin and eyes and juxta-cutaneous mucous membranes proves the absence of a possible primary growth there and inquiry elicits positive certainty that the patient has never had any skin lesion which might have been the primary source the primary visceral origin of a melanoma cannot be accepted. I know of no reported cases fully satisfying these strict requirements

MELANOMAS IN ANIMALS

Cutaneous melanomas are well known in horses dogs cattle and pigs (Feldman) but have seldom been observed in other animals. Feldman referred to one example in a cat, Orr and Polson saw one in a rabbit and melanotic tumours, some with a heritable tendency, occur also in fish (Haddow and Blake Gordon and Smith). Old grey or white horses are peculiarly prone to cutaneous melanomas the commonest sites of which are about the base of the tail and the genitalia. These growths are apparently not preceded by benign moles comparable to the human ones. Old dogs also frequently develop cutaneous melanotic growths these are sometimes benign multiple or single and sometimes malignant the malignant ones often arising in previously indolent growths of the benign type. The structure of the benign growths however is unlike that of human pigmented moles consisting usually of projecting pedunculated masses clothed by intact heavily pigmented epidermis underlain by thickened dermis containing few or many rounded or elongated cells loaded with pigment many of them clearly only phagocytes. Malignant growths show a diversity of structure and a capacity for metastasis similar to the human ones. Feldman gives references to occasional instances of melanotic tumours of the meninges or brain in animals but whether primary or secondary is uncertain. I have not read of an intra-ocular melanoma in an animal.

Closer study of melanosis and melanomas in animals is needed it will surely help in the solution of some of the vexed problems of histogenesis in this field

GENERAL CONCLUSIONS

The views expressed above regarding the histogenesis of the several groups of melanomas may now be epitomized. In my opinion naevus cells and malignant melanomas of the skin are certainly of epidermal origin this does not exclude the participation of nerves and nerve-endings in the malformation which a pigmented mole is nor the participation of tactile epidermal cells in the formation

of melanotic tumours. The origin of the pigment cells of the meninges, from which primary meningeal melanomas arise, is undetermined, there is no evidence that they are derived from neuro epithelium or that they are not mesenchymal, and the meningeal tumours behave differently from cutaneous and ocular ones. The histogenesis of the choroidal pigment-cells and of the intra ocular melanotic tumours is still unsettled, it is possible that they may be derived from the pigmented layer of the retina, or from the mesenchyme of the choroid which is the homologue of the meninges, or from either. Some epibulbar melanomas almost certainly arise from non epithelial episcleral pigment-cells comparable with those of the meninges, but conjunctival epithelial naevus-cell melanomas also occur.

I conclude, as I began, by saying that I think it a mistake to regard all melanotic tumours as comparable and to try to devise a unified histogenetic hypothesis to embrace them all. Their several tissues of origin differ greatly in development and function, and the corresponding several groups of tumours differ significantly from one another in structure and behaviour. It may be contended that the essential community of all pigmented tissues is shown by cases (such as my Case III, and those of Berblinger, Bjorneboe, and others) in which developmentally abnormal pigmentation affects skin, eyes and meninges simultaneously. This argument, strong though it appears to be, is not necessarily valid. If melanin production is merely a common function of several distinct kinds of tissues then factors disturbing that function might well do so simultaneously in those several tissues—just as diabetes may cause visible disturbances of glycogen or lipid metabolism in several distinct kinds of cells.

It is not impossible that further research may lead to some unification of our concepts of melanin formation and of the histogenetic relationships of melanotic cells and their tumours. At present, however, our knowledge is too incomplete to allow us to frame any unified hypothesis, and attempts to do so are forced and speculative.

REFERENCES

- Affleck D H (1936) *Amer J Cancer* 27, 120
 Akelatis A J E (1935) *Amer J Path* 11 591
 Albers E S (1940) *Amer J Ophth* 23 779
 Berblinger, W (1915) *Virchows Arch* 219, 328
 Bishop E L (1932) *Amer J Cancer* 16 522
 Bjorneboe M (1934) *Frankfurt Z Path* 47 363
 Boit H (1907) *Frankfurt Z Path*, 1 248
 Bonser G M (1946) *Brit J Radiol* 19 229
 Bromberg Y M and Brzezinski A (1944) *J Obst Gyn* 51 147
 Cairns F D (1922) *Brit J Surg* 10 290
 COLLINS, E T (1926) Intra ocular melanomata *Trans Ophth Soc UK* 46 86
 Davidsohn C (1909) *Verh Dtsch path Ges* 13 287
 Dawson E K, Innes J R M, and Harvey W F (1939) *Edinb Med J* 46 695
 Dawson E K (1946) *Brit J Radiol* 19 219
 Dawson H G W (1922) *Brit Med J* ii 757
 DAWSON, J W (1925) *The Melanomata their Morphology and Histogenesis* Edinburgh (Reprinted from *Edinb Med J* Oct 1925) (An indispensable classic)
 Dieckmann H (1930) *Virchows Arch* 275 785
 DUKE ELDER W S (1940) *Text book of Ophthalmology* Vol III, pp 2471-2516 London (A useful well illustrated account of the ocular melanomas)

- Elsberg C A (1928) *Surg Gyn Obst* 46 1
- Feldman W H (1932) *Neoplasms of Domesticated Animals* Chapter XVI Philadelphia
- Feyrter F (1938) *Virchows Arch* 301 417
- Foot N C (1931 and 1932) *Amer J Path* 1931 7 619 1932, 8 309 and 321
- Foot, N C and Zeek P (1931) *Amer J Path* 7 605
- Goldzieher M (1913) *Zbl allgem Path* 24 397
- Gordon M and Smith G M (1938) *Amer J Cancer* 34 255 and 543
- Gotschalk H C Tessmer C F and Smith J W (1940) *Arch Path* 30 762.
- Grahl F (1906) *Beitr path Anat* 39 66
- Haddow A and Blake I (1933) *J Path Bact* 36 41
- Hamburger L P (1898) *Johns Hopk Hosp Bull* 9 50
- Hassin G B and Bassoe P (1929) *Arch Neurol Psych* 21 1037
- Heilmann P (1931) *Zbl allgem Path* 52 369
- Hewer T F (1935) *J Path Bact* 41 473
- Hirschberg, A (1906) *Virchows Arch* 186 229
- Houwer A W M (1928) *Trans Ophth Soc U.K.* 48 167
- Johnston K B (1929) *Brit J Ophth* 13 498
- Kawashima K (1910) *Virchows Arch* 201 297
- Kiel F (1922) *Zbl allgem Path* 33 393
- Kraft J (1929) *Z Krebsforsch* 29 74
- LAIDLAW G F (1932) The Dopa reaction in general pathology *Amer J Path* 8 477
(A valuable outline)
- Lua M (1914) *Arch f Psych* 53 895
- MacLachlan W W G (1914 and 1915) *J Med Res* 1914 24 433 1915 28 93
- Mann I C (1926) *Trans Ophth Soc U.K.* 46 132
- Masson P (1926) *Ann Anat path* 3 417 and 657
- Minelli D S (1906) *Virchows Arch* 183 129
- Montgomery H and Kahler J E. (1939) *Amer J Cancer* 36 527
- Mori T (1913) *Frankfurt Z Path* 12 2
- New G B and Hausel F K (1921) *J Amer Med Assoc* 77 19
- Nicholson, G W (1918) *J Path Bact* 22 252.
- Nicholson, G W (1922 and 1923) *Guv's Hosp.-Rep* 1922 72 333 1923, 73 37
- Nicholson G W (1936) *J Path Bact* 43 209
- Omodei Zorini A (1924) *Virchows Arch* 250 566
- Orr J W and Polson C J (1938) *Amer J Cancer* 32 114
- Peller S (1941) *Cancer Res* 1 538
- Rolleston H D (1912) *Diseases of the Liver Gall-bladder and Bile Ducts* London
- Rosenthal S R (1931) *Amer J Cancer* 15 2288
- Schmidt, J (1912) *Frankfurt Z Path* 9 400
- Schopper K J (1913) *Frankfurt Z Path* 13 77
- Selig, S (1934) *Amer J Cancer* 20 594
- Smith R M (1927) *Med J Austral* 1 683
- SPENCER W G (1923) Melanosis (melanin melanoma melanotic cancer) *Brit Med J* ii 937 (An interesting review)
- Stout A P (1938) *Amer J Cancer* 33 196
- Taylor C. E., and Tuttle H K. (1944) *Arch Path* 38 60
- Temple L. J (1941) *Brit Med J* ii 511
- Terry T L. and Johns, J P (1935) *Amer J Ophth* 18 903
- Trinca, A J and Willis, R A (1936) *Med J Austral.*, ii 222.
- Virchow R (1859) *Virchows Arch.*, 16 180
- Webb-Johnson A E. and McLeod C. E. A (1924) *Brit Med J.*, i 314
- Weber I P Schwarz E., and Hellenschmied R (1930) *Brit Med J.*, i 537
- Webster J P., Stevenson T W and Stout A P (1944) *Surg Clinics N Amer* p 319
- Wilbur D L. and Hartman, H R (1931) *Ann Int Med.*, 5 201
- Willis, R A (1934) *The Spread of Tumours in the Human Body* London
- Willis, R A (1936) *J Path Bact* 43 223

CHAPTER 59

CHORDOMA

HISTORICAL OUTLINE

IN 1857, several examples of small gelatinous masses projecting into the cranial cavity from the clivus were described by Luschka, Hasse, Zenker and Virchow. Virchow regarded these as cartilaginous, and, because of the vacuolated character of their cells, named them "ecchondrosis physaliphora". In 1858, H. Muller recorded a careful study of the notochord in the developing skull, and expressed the view that the so called "ecchondroses" were really derived from notochordal remnants. Subsequent writers, however, adhered to Virchow's view, and it was not until 1894 that confirmation of Muller's opinion was advanced by Ribbert. Since then, it has been generally accepted that the gelatinous nodules occasionally found projecting from the clivus or dorsum sellae are "ecchordoses" consisting of heterotopic chordal tissue, and that true tumours, chordomas, arise from these or from the intra osseous remains of chordal tissue. The first recorded spheno occipital "ecchondroses" large enough to cause symptoms were those of Klebs (1864) and Grahl (1903) the latter so large a mass that it probably was a chordoma. The first cranial tumour specifically designated a 'malignant chordoma' was that of Fischer and Steiner (1907) and the first record of projection of such a tumour into the pharynx from the skull base was that of Linck (1909).

The first to report chordomas in the sacro coccygeal region were Feldmann (1910) and Mazzia (1910) although Morpurgo reported such a growth in an osteomalacic rat in 1907. Thereafter, increasing numbers of sacro coccygeal chordomas were reported and it soon became apparent that these were commoner than their cranial counterparts. Chordomas of the vertebral column, the least frequent site, have been well recognized only recently (Cappell, 1928, Guthert, 1939). The most valuable reviews of the subject of chordoma are those of Stewart (1922), Stewart and Morin (1926), Cappell (1928), Guthert (1939) and Harvey and Dawson (1941). Other noteworthy papers include those of Owen and co authors (on chordomas of the cervical vertebrae) and Hutton and Young.

THE DEVELOPMENT OF THE NOTOCHORD

The correctness of Muller's observations nearly a century ago on the development of the spheno occipital part of the notochord and its relation to ecchordoses has since been verified repeatedly. Embryological studies show that the upper end of the young notochord closely approaches the inner surface of the sphenoid and may lie in contact with the dura overlying the dorsum sellae, that more caudally in the basilar part of the developing occipital bone, the notochord approaches the lower or pharyngeal surface of the bone and part of it may lie between the basilar plate and the wall of the pharynx and that in any of these situations remnants of chordal tissue frequently persist in adults (Williams, Huber

- Elsberg, C A (1928) *Surg Gyn Obst* 46 1
- Feldman W H (1932) *Neoplasms of Domesticated Animals* Chapter XVI Philadelphia
- Feyrter F (1938) *Virchows Arch* 301 417
- Foot N C (1931 and 1932) *Amer J Path* 1931 7 619, 1932 8 309 and 321
- Foot, N C and Zeek P (1931) *Amer J Path* 7 605
- Goldzieher M (1913) *Zbl allgem Path* 24 397
- Gordon M and Smith G M (1938) *Amer J Cancer* 34 255 and 543
- Gotschalk H C Tessmer C F and Smith J W (1940) *Arch Path* 30 762
- Grahl F (1906) *Beitr path Anat* 39 66
- Haddow A and Blake I (1933) *J Path Bact* 36 41
- Hamburger L P (1898) *Johns Hopk Hosp Bull* 9 50
- Hassin G B and Bassoe P (1929) *Arch Neurol Psych* 21 1087
- Heilmann P (1931) *Zbl allgem Path* 52 369
- Hewer, T F (1935) *J Path Bact* 41 473
- Hirschberg A (1906) *Virchows Arch* 186 229
- Houwer A W M (1928) *Trans Ophth Soc UK* 48 167
- Johnston K B (1929) *Brit J Ophth* 13 498
- Kawashima K (1910) *Virchows Arch* 201 297
- Kiel E (1922) *Zbl allgem Path* 33 393
- Kraft J (1929) *Z Krebsforsch* 29 74
- LAIDLAW G F (1932) The Dopa reaction in general pathology *Amer J Path* 8 477
(A valuable outline)
- Lua M (1914) *Arch f Psych* 53 895
- MacLachlan W W G (1914 and 1915) *J Med Res* 1914 24 433 1915 28 93
- Mann I C (1926) *Trans Ophth Soc UK* 46 132
- Masson P (1926) *Ann Anat path* 3 417 and 657
- Minelli D S (1906) *Virchows Arch* 183 129
- Montgomery H and Kahler J E (1939) *Amer J Cancer* 36 527
- Mori T (1913) *Frankfurt Z Path* 12 2
- New G B and Hausel F K (1921) *J Amer Med Assoc* 77 19
- Nicholson, G W (1918) *J Path Bact* 22 252
- Nicholson, G W (1922 and 1923) *Guys Hosp Rep* 1922 72, 333 1923 73 37
- Nicholson G W (1936) *J Path Bact* 43 209
- Omodei Zorini A (1924) *Virchows Arch* 250 566
- Orr J W and Polson C J (1938) *Amer J Cancer* 32 114
- Peller S (1941) *Cancer Res* 1 538
- Rolleston H D (1912) *Diseases of the Liver Gall bladder and Bile Ducts* London
- Rosenthal S R (1931) *Amer J Cancer* 15 2288
- Schmidt, J (1912) *Frankfurt Z Path* 9 400
- Schopper K J (1913) *Frankfurt Z Path* 13 77
- Selig, S (1934) *Amer J Cancer* 20 594
- Smith R M (1927) *Med J Austral* 1 683
- SPENCER W G (1923) Melanosis (melanin melanoma melanotic cancer) *Brit Med J* 11 907 (An interesting review)
- Stout A P (1938) *Amer J Cancer* 33 196
- Taylor C F and Tuttle H K (1944) *Arch Path* 38 60
- Temple L J (1941) *Brit Med J* 11 511
- Terry T L and Johns, J P (1935) *Amer J Ophth* 18 903
- Trinca A J and Willis, R A (1936) *Med J Austral* 11 222
- Virchow R. (1859) *Virchows Arch* 16 180
- Webb-Johnson A E. and McLeod C E. A. (1924) *Brit Med J* 1 314
- Weber F P Schwarz E and Hellenschmied R (1930) *Brit Med J*, 1 537
- Webster J P., Stevenson T W and Stout A P (1944) *Surg Clinics N Amer* 8 319
- Wilbur D L. and Hartman H R (1931) *Ann Int Med* 5 201
- Willis R A (1934) *The Spread of Tumours in the Human Body* London
- Willis R A (1936) *J Path Bact* 43 223

CHORDOMA

The liver contained 3 small gelatinous metastases showed typical chordoma with irregular clumps of vacuolated cells and plentiful extracellular mucus

Case III—Necropsy on an elderly woman who was admitted to hospital in extremis and with no recorded history disclosed in addition to fatal pyelo-cystitis and pneumonia, a soft lobulated gelatinous and haemorrhagic tumour 8 centimetres in diameter projecting into the pelvis from the sacrum parts of the lower 4 segments of which were destroyed by the growth. *Microscopical examination* showed typical chordoma

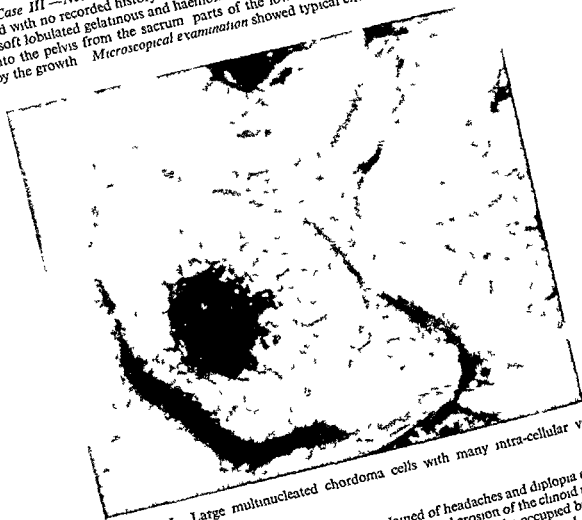


FIG. 454—*Case I* Large multinucleated chordoma cells with many intra-cellular vacuoles ($\times 750$)

Case IV—In June 1938 a man aged 50 complained of headaches and diplopia of 2 years duration. Skiagrams showed enlargement of the sella and erosion of the clinoid processes and operation (Mr H C Trumble) showed the pituitary fossa to be occupied by a tumour consisting of a fibrous wall enclosing degenerated tissue. This was evacuated but proved unsatisfactory for microscopical diagnosis. Improvement followed and was maintained until November 1940 when diplopia recurred and some nasal obstruction was noticed. In April 1941 examination showed a lobulated mass projecting into the vault of the nasopharynx and skiagrams showed increased destruction of bone around the sella and some destruction of the left petrous bone. The patient returned to his home in the country where he died in December 1941 at the age of 53. *Necropsy* by Dr J R Searls of Bainsdale Victoria disclosed a large extradural mass of gelatinous and haemorrhagic growth in the pituitary region extensively destroying the body of the sphenoid and the basilar plate and extending a considerable distance down the spinal canal but without compression of the cord. *Microscopical examination* showed typical chordoma

Case V—In January 1942 a man aged 51 complained of upper dorsal pain of 18 months duration and recent symptoms of paraplegia. Skiagrams disclosed a destructive lesion

Newland and Woollard) That these remnants are the origin of ecchordoses, and of chordomas is clear to anyone familiar with them

The persistence of aberrant buds of notochordal tissue in the sacro coccygeal region also, described by a number of workers (e.g. Berard and co workers 1922 and Horwitz, 1941), can easily be verified in median and paramedian sections of this region in fetuses or infants, and there is little doubt that remnants of these are the source of sacro coccygeal chordomas. In the spinal column the rarest site of chordomas, aberrant chordal tissue has seldom been seen. It seems very probable then that the usual source of chordomas is from such aberrant residual tissue as we are familiar with at the two extremities of the axis, and rarely, if ever from the normal intervertebral discs

Ecchordoses

Ecchordoses of the sphenoid-occipital region are not uncommon when carefully sought. Ribbert claimed to have found them in 2 per cent of necropsies, and Stewart and Morin who reviewed 24 recorded examples, found 4 in 350 necropsies. They were rather less frequent in my necropsy experience, I found 5 ecchordoses in over 1 000 necropsies in which they were looked for. They appear as soft gelatinous pedunculated masses usually only a few millimetres but sometimes 2 centimetres or more in diameter, often with flat inner surfaces where they have lain against the brain stem. The pedicle is often very narrow even filamentous, the little mass being moored loosely to the dorsum sellae by a thread. The pedicle which consists also of chordal tissue always transverses a small aperture in the dura mater and vertical sections through the aperture will show that the ecchordosis is continuous with remnants of similar tissue in the bone. Microscopically an ecchordosis like the notochordal remains from which it springs consists of irregular vacuolated cells single or in aggregates set in an abundant mucoid matrix. Ecchordoses are quiescent chordal ectopias and should be distinguished from true tumours to which however, they may give origin.

FIVE PERSONALLY STUDIED CHORDOMAS

The following five personally studied cases of chordoma exemplify most of the features of this disease. Three of the tumours were sacral one was cranial and one was upper thoracic in position.

Case I (Reported in 1930)—The tumour a huge sacral chordoma with massive extension into the thigh had produced symptoms for 4½ years before the woman's death at the age of 41. Multiple exostoses of many bones had also been present since childhood. *Necropsy* showed that the huge gelatinous, partly calcified sacral tumour which weighed 200 ounces had probably invaded the main iliac veins and that there were multiple gelatinous metastases in the lungs liver heart spleen kidneys thyroid and skin. *Microscopical examination* (Fig. 454)—The tumours consisted of prominently vacuolated cells with many multinucleated giant forms, and abundant extra-cellular mucus. Young metastases in the lungs showed prominent hyaline capsules like those depicted by Cappel.

Case II (Reported by Cat and Willis 1932 and 1933)—A man 36 years old at death had had symptoms of his sacral tumour for 5 years. *Necropsy* showed the large gelatinous tumour to occupy most of the pelvic cavity and to have destroyed most of the sacrum.

or other tissues resembling chordoma, as was probably the case in the sacral tumour of a 7 months foetus described by Hennig (1900) Harvey and Dawson also expressed such doubts in the legends to their figures 34, 38, 39 and 40. However, that true chordoma does occur in children is shown by such cases as that reported by Ellis (1935).

The average age at which the patients first come under observation differs decidedly according to the site of the tumours: the mean ages of 20 cranial cases reviewed by Stewart and Morin was 35 years, and of 28 sacral cases 51 years. This seems to be a greater difference than can be accounted for by earlier onset of symptoms in the cranial cases.

(3) Sex

The 220 cases reviewed by Harvey and Dawson comprised 144 males and 76 females. The preponderance of males is more marked in the sacral than in the cranial group. It has been suggested that *trauma* plays a part in the causation of chordoma, and that this may account for the different liability of the sexes, but this is very doubtful. (See Hueper, 1942.)

(4) Co-existing anomalies

Several reported cases of chordoma showed other skeletal disease. In Cappell's second case, a chordoma of the fourth cervical vertebra was accompanied by an independent ecchordosis of the dorsum sellae; my Case I (above) had multiple exostoses of many bones; and Harvey and Dawson mentioned a case of cranial chordoma associated with multiple chondromas of the left arm. These cases are insufficient to suggest more than a possibility that some constitutional tendency to skeletal anomalies may underlie the genesis of chordomas.

THE GROSS STRUCTURE OF CHORDOMAS

The typical chordoma is a slowly growing well defined lobulated tumour, consisting of soft gelatinous tissue, often with areas of haemorrhage, cystic degeneration or calcification, and sometimes with areas of more solid white tissue. It invades, distends and destroys the neighbouring bone, and extends into adjacent regions, the nasopharynx or orbits or the retroperitoneal tissues or thigh. A huge size may be attained by the sacral tumours: e.g. that recorded by Stewart and Morin had a circumference of 80 centimetres, the tumour of my Case I weighed about 200 ounces, and that of Graf's case 9 kilograms. The sphenoccipital growths of course do not attain such large sizes; they usually project prominently into the cranial cavity, sometimes into the pharynx also, as in Case IV, and only rarely into the pharynx only.

THE MICROSCOPICAL STRUCTURE OF CHORDOMAS

The microscopical appearance of chordoma is rather variable but in representative pieces of tissue easy of recognition. The cells are usually aggregated in irregular groups, separated by stromal connective tissues or by the mucoid matrix of the tumour itself. They vary greatly in size and shape but in compact healthy regions of the growth fairly uniform polyhedral cells may be grouped to

of the first and second dorsal vertebrae and at operation by Mr Balcombe Quick a quantity of friable growth which was compressing the cord was removed. In August 1944 there was massive recurrence in the muscles of the back in spite of intensive X ray irradiation. *Microscopically* the tumour was a chordoma.



FIG 455—Case II Typical chordoma ($\times 120$)

SITE AGE AND SEX DISTRIBUTION OF CHORDOMAS

(1) Site

Harvey and Dawson's review of 240 cases of chordoma showed the following distribution

Cranial	-	-	-	-	-	88	(37 per cent)
Vertebral	-	-	-	-	-	30	(12 „)
Sacro-coccygeal	-	-	-	-	-	122	(51 „)

Horwitz's review of 245 cases gave the corresponding percentages as 33 12 and 55

(2) Age

According to Harvey and Dawson the age distribution of 211 cases was

Decades	-	-	-	-	1	2	3	4	5	6	7	8	9
No of cases	-	-	-	-	14	7	21	44	35	46	40	2	2

Thus no age is exempt and there is no well-defined peak of distribution in any particular decade. There is room for doubting the correctness of the diagnosis in some of the incompletely investigated sacro-coccygeal tumours in infants, some of these may have been teratomatous with extensive areas of cartilaginous

CHORDOMA

924

- Graf L (1944) *Arch Path* 37 136
 Grahl O (1903) (Cited by Stewart)
 Guthert H (1939) *Z Krebsforsch* 48 557
 HARVEY, W F, and DAWSON, E K (1941) Chordoma, *Edinb Med J* 48 713 (A)
 useful brief review with many good illustrations)
 Hasse (1857) *Virchows Arch* 11 395
 Hennig L (1900) *Beitr path Anat* 28 593
 Horwitz T (1941) *Arch Path* 31 354
 Huber C C (1912) *Anat Rec* 6 373
 Hueper W C (1942) *Occupational Tumors* p 700 Springfield
 Hutton A J, and Young A (1929) *Surg Gyn Obst*, 48 333
 Klebs E (1864) *Virchows Arch* 31 396
 Lewis N D C (1921) *Arch Int Med* 28 434
 Linck A (1909) *Beitr path Anat* 46 573
 Luschka H (1857) *Virchows Arch* 11, 8
 Mazzia O (1910) (Cited by Stewart)
 Morpurgo B (1907) *Z ration Med* 2 202
 Muller H (1858) *Z ration Med* 2 202
 Newland H S and Woollard H H (1929) *J Coll Surg Austral* 2 157
 Owen C I Hershey L N and Gurdjian E S (1932) *Amer J Cancer*, 16, 830
 Peters W (1919) *Disch Z Chir* 151 191
 Pototschnig G (1919) *Beitr path Anat* 65 356
 Ribbert H (1894) *Zbl allgem Path* 5 457
 STEWART, M J (1922) Malignant sacrococcygeal chordoma, *J Path Bact*, 25, 40 (A)
 valuable review)
 STEWART, M J, and MORIN, J E (1926) Chordoma a review with report of a new
 sacrococcygeal case *J Path Bact* 29 41
 Virchow R (1857) (Cited by Stewart)
 Williams, L W (1908) *J Anat* 8 231
 Willis, R A (1930) *J Path Bact*, 33 1035
 Willis R A (1933) *Austral N Z J Surg* 3 93
 Zenker, F A (1857) *Virchows Arch* 12 108

resemble cords or clumps of epithelium. The characteristic cytoplasmic and intercellular vacuolation, little in evidence in the smaller polyhedral cells, becomes prominent in the larger 'physaliphorous' cells, in which cell outlines may be lost and the appearance may be that of a highly vacuolated syncytium. Vacuolated cells may assume signet ring forms. In areas of greatest mucus formation only scattered islets of cells remain in a sea of mucinous matrix. This extra-cellular material gives the usual staining reactions of mucin but the intra cellular vacuoles often appear empty or their contents fails to stain selectively. Intra cellular glycogen, described by some writers, is difficult to demonstrate in most tumours. Multinucleated cells are not uncommon and occasionally as in my Case I, they attain huge sizes and contain many nuclei. Mitotic figures are rare. Nuclear vacuolation has been described but is unusual. Grouping of flattened cells in whorls is a rare feature well depicted by Stewart and Morin. In some areas of compact growth the cells assume fusiform shapes presumably from compression. Isolated clumps of tumour tissue sometimes develop a distinct hyaline sheath delimitating the tumour from the surrounding tissues and resembling the sheath of a young notochord (Cappell Willis, Harvey and Dawson). Some of these various features are depicted in Figs 454 and 455.

THE METASTASIS OF CHORDOMAS

Chordoma, although an invasive almost always fatal growth does not often metastasize widely. Metastases in lymph glands were reported by Peters (1919) Lewis (1921) and Pototschnig (1919) and Pototschnig's case also had metastases in the liver. Stewart's case had large secondary growths in the soft tissues of the buttock and over the scapula but no visceral metastases were found at necropsy. My Case I had widely disseminated blood borne metastases in many organs and Case II had small metastases in the liver only doubtless due to transport via the portal blood stream from the pelvis. Graf's case had metastases in lymph glands liver lungs and skin.

PROGNOSIS AND DURATION OF CHORDOMA

The ultimate outlook of cases of chordoma is uniformly bad but many of the tumours are of slow growth and some of the patients survive for many years. Stewart and Morin found the average duration of cranial cases from the onset of symptoms to be 2.8 years and of sacral cases 6.4 years. Even when complete removal of a growth appears to have been achieved prognosis must be guarded, in Stewart's case recurrence ensued after 5 years apparent freedom from disease following excision. The total duration in this case from first appearance of the tumour to the patient's death was 19 years.

REFERENCES

- Bérard L. Dunet C. L. and Peyron A. (1922) *Bull Assoc fran, Cancer* 11 28
 CAIFFILL, D. F. (1928) Chordoma of the vertebral column with three new cases. *J Path Bact* 31 797 (A valuable well illustrated study)
 Cato E. T. (1932) *Austral N Z J Surg* 1 425
 Ellis, V. H. (1935) *Brit J Surg* 23 25
 Feldmann I. (1910) *Beitr path Anat* 48 630
 Fischer B. and Steiner (1907) *Beitr path Anat* 40 109

Wells tabulated a number of records of certainly or probably congenital nephroblastomas. There exist reports of several specimens found in foetuses, e.g. Nicholson's (1931). All large series show a majority of cases with symptomatic onset in the first 3 years of life, and cases with onset after the age of 10 are very rare (Hedren, McCurdy, Herzog).

"Mixed tumours" have often been reported in adults but very few of these withstand critical examination. Thus the adult cases reported by Hedren (Case 3), Kilbane and Lester, Papin *et al*, Busser *et al*, Hamm, and Sparks can be dismissed, the tumours were probably carcinomas of ordinary adult type with anaplastic



FIG. 456—Case 1 Nephroblastoma. Cellular tissue differentiating into both tubules and non epithelial tissue ($\times 100$).

areas. So also was the tumour reported by Moore in a man aged 56, in which the areas of bony tissue were probably the result of stromal metaplasia in a long standing carcinoma. Bosse rightly warned against mistaking glomerulus like formations for true glomeruli in renal or other adenocarcinomas. Muus's third case appears to have been a genuine one of mixed tumour in a woman aged 34. The tumour in Busse's second case, a large rhabdomyoma of the renal capsule in a woman aged 57 may have been related to the embryonic mixed tumour, though no epithelial elements were found in it. In Hoisholt's case also, a tumour from a youth aged 18 contained spindle celled growth and cartilage but no epithelium. In Hasner's third case in a man aged 45, while no histological details are given, the two good photographs certainly depict both tubules and striated muscle fibres. I have examined one undoubted specimen of embryonic renal tumour from a man aged 30, thoroughly studied by H. A. Sissons.

CHAPTER 60

EMBRYONIC TUMOURS OF KIDNEY AND LIVER AND GENERAL COMMENTS ON EMBRYONIC TUMOURS

WE HAVE already discussed several distinct kinds of truly embryonic tumours—neuro-epithelioma and medulloblastoma of the brain neuroblastoma of the sympathetic system retinal neuro-epithelioma or retinoblastoma, and rhabdomyosarcomas of the pelvic organs and some other parts. Two other kinds of truly embryonic tumours remain for consideration, namely nephroblastoma or embryonic tumour of the kidney and hepatoblastoma or embryonic tumour of the liver. Some general comments on the significance of embryonic tumours will be added.

EMBRYONIC TUMOURS OF THE KIDNEY NEPHROBLASTOMA

Many names have been applied to the embryonic renal tumours—adenosarcoma myo-sarcoma" mixed tumour, Wilms's tumour', 'embryoma', embryonic nephroma and nephroblastoma. These of course do not imply different kinds of tumours but merely structural variants or different notions regarding histogenesis. It is now clear that there is but one entity embryonic renal tumour, appropriately called also 'nephroblastoma' since it arises from and consists of immature renal blastema.

The earliest descriptions of these growths include those of Eberth (1872) Cohnheim (1875) Marchand (1878) Eve (1882) and Williams (1882). Eve however recorded a bilateral Hunterian specimen which must have dated from 1790 or earlier. Good reports and reviews include those of Muus (1899) Hedren (1907) and Kretschmer and Hibbs (1931).

The following case provided a typical specimen.

Case I—History—A male child who had weighed 4 pounds when delivered by Caesarean section because of maternal renal disease developed normally until 15 months old when he began to suffer from haematuria and to pass small pieces of flesh. Microscopically these consisted of necrotic cellular tumour tissue: the right kidney was palpably enlarged and nephrectomy was performed. The child remained well 7 years later at the age of 8½. *Specimen*—The kidney was largely replaced by a well-defined lobulated tumour 9 × 8 × 6 centimetres confined within the renal capsule and showing a compressed rim of kidney tissue at parts of the periphery. It consisted of homogeneous white tissue except for some haemorrhagic changes in polypoid masses of growth which filled and distended the calices and pelvis. *Histological structure* is shown in Figs. 456–461. It includes undifferentiated cellular tissue partly epithelial and partly non-epithelial tubules and pro-glomeruli in all stages of formation, much young connective tissue, smooth muscle fibres and occasional groups of striated muscle fibres. The polypoid masses in the pelvis are clothed in most places by a layer of pelvic epithelium which dips down deeply into the intervening crypts of this part of the tumour.

(1) Age incidence

Most of these tumours are discovered in infancy or early childhood and there is no doubt that in a high proportion of cases they were already present at birth.

(a) Invasion of veins

This is sometimes conspicuous, and is of course an important factor in prognosis. Examples of extensive growth within the renal veins and inferior vena cava and even into the heart are recorded by Merkel, Engelken, Muus, Rosenstein, Loughnane and Dew, in Dew's case, the left sided renal tumour extended to the cord and testis within the spermatic veins.

(b) Metastases

These are most frequent in the lungs but may occur also in liver, bones, lymph nodes and peritoneum. Noteworthy reports include those of Merkel, Engelken, Hedren (Case 5), Loughnane, Fraser, Wollstein, Kretschmer and Hibbs, Grewal, and Mintz, the last two writers particularly describing metastases in bones. In many cases the structure of the metastases has been as complex as that of the primary tumour, showing the immaturity and multipotentiality of the neoplastic blastema cells transported.

(6) Embryonic renal tumours in animals

Tumours undoubtedly comparable with the embryonic tumours of the human kidney occur in the pig (Feldman 1932 Chapter XXI), ox (Feldman Fig 188) sheep (Feldman, 1933), rabbit and hare (Bell and Henrici, Scott, Polson, Eisler), rat (Bullock and Curtis, Ratchiffe) and fowl (McKenney, Feldman and Olson). Nephroblastomas are the commonest of all tumours in pigs and are also relatively frequent in chickens. Most of the affected animals are young. As in humans, most of the tumours are unilateral and solitary, but bilateral growths sometimes occur, as in 8 of Feldman's 46 tumours of swine and in the fowl reported by Feldman and Olson. In structure the growths generally resemble their human counterparts, showing a mixture of undifferentiated tissue and differentiating tubular, glomerular and connective tissues. (Many excellent figures by Feldman.) Conspicuous squamous change, as in Feldman and Olson's specimen is infrequent, and striated muscle fibres, as in one of Bullock and Curtis's rats, have rarely been seen. Metastasis has been observed in the pig, ox and sheep rarely in the fowl and not at all in the rodents, in which the tumours appear to be relatively benign.

EMBRYONIC TUMOURS OF THE LIVER HEPATOBLASTOMA

Tumours clearly comparable with the embryonic tumours of the kidney occasionally arise in the liver. They occur in the foetus or young infant, and consist of embryonic liver tissue, sometimes accompanied by heterotopic tissues also. In considering these tumours three sources of confusion are to be avoided, namely (i) metastatic neuroblastoma must not be mistaken for a primary liver tumour, (ii) congenital angiomas must be distinguished from hepatoblastoma and (iii) primary carcinoma of adult type occurring in childhood or youth should be distinguished from embryonic hepatoma. For a good discussion of the several kinds of malignant hepatic tumours in infancy, consult Wells's paper (1940). The tumour in a girl aged 9 reported by Kilfoy and Terry is a good example of a hepatic carcinoma probably not of embryonic origin, and the same applies to many of the other cases tabulated by them. It must be admitted,

(2) Sex incidence

In most series males are about twice as numerous as females (Kretschmer and Hibbs, McCurdy Herzog)

(3) Site

The tumours are usually single and unilateral, but multiple or bilateral growths occur as in Eberth's Cohnheim's and Merkel's cases the Hunterian specimen referred to by Eve Hedren's first case, 2 of the 17 cases reported by Kretschmer and Hibbs and in 8 of the 107 cases reviewed by Herzog Hedrén's case was remarkable in showing 2 separate tumours in the right kidney 3 in the left and also microscopic foci of undifferentiated tissue in other parts of the kidneys



FIG. 457.—Case 1 Nephroblastoma. Incompletely differentiated epithelial clumps in mesenchyme like connective tissue ($\times 100$)

(4) Structure and histogenesis

The structure varies greatly. In most tumours embryonic renal tissue showing different degrees of differentiation predominates, while various heterotopic tissues may also appear in varying proportions (See Figs 456-461)

(a) Undifferentiated tissue

This is often plentiful and constitutes the bulk or even the whole of some tumours. It resembles and undoubtedly corresponds to early embryonic renal blastema. All stages in the transformation of this tissue into differentiated renal or heterotopic tissues can be traced.

(b) Epithelial structures

These show great diversity of form including undifferentiated epithelial

(a) Invasion of veins

This is sometimes conspicuous, and is of course an important factor in prognosis. Examples of extensive growth within the renal veins and inferior vena cava and even into the heart are recorded by Merkel, Engelken, Muus, Rosenstein, Loughnane and Dew, in Dew's case, the left sided renal tumour extended to the cord and testis within the spermatic veins.

(b) Metastases

These are most frequent in the lungs but may occur also in liver, bones, lymph nodes and peritoneum. Noteworthy reports include those of Merkel, Engelken, Hedren (Case 5), Loughnane, Fraser, Wollstein, Kretschmer and Hibbs, Grewal, and Mintz, the last two writers particularly describing metastases in bones. In many cases the structure of the metastases has been as complex as that of the primary tumour, showing the immaturity and multipotentiality of the neoplastic blastema cells transported.

(6) Embryonic renal tumours in animals

Tumours undoubtedly comparable with the embryonic tumours of the human kidney occur in the pig (Feldman, 1932, Chapter XXI), ox (Feldman Fig 188), sheep (Feldman, 1933), rabbit and hare (Bell and Henrici, Scott, Polson, Eisler), rat (Bullock and Curtis, Ratchiffe) and fowl (McKenney, Feldman and Olson). Nephroblastomas are the commonest of all tumours in pigs, and are also relatively frequent in chickens. Most of the affected animals are young. As in humans, most of the tumours are unilateral and solitary, but bilateral growths sometimes occur, as in 8 of Feldman's 46 tumours of swine and in the fowl reported by Feldman and Olson. In structure the growths generally resemble their human counterparts, showing a mixture of undifferentiated tissue and differentiating tubular, glomerular and connective tissues. (Many excellent figures by Feldman.) Conspicuous squamous change, as in Feldman and Olson's specimen, is infrequent, and striated muscle fibres, as in one of Bullock and Curtis's rats, have rarely been seen. Metastasis has been observed in the pig, ox and sheep, rarely in the fowl, and not at all in the rodents, in which the tumours appear to be relatively benign.

EMBRYONIC TUMOURS OF THE LIVER HEPATOBLASTOMA

Tumours clearly comparable with the embryonic tumours of the kidney occasionally arise in the liver. They occur in the foetus or young infant, and consist of embryonic liver tissue, sometimes accompanied by heterotopic tissues also. In considering these tumours three sources of confusion are to be avoided, namely (i) metastatic neuroblastoma must not be mistaken for a primary liver tumour, (ii) congenital angiomas must be distinguished from hepatoblastoma, and (iii) primary carcinoma of adult type occurring in childhood or youth should be distinguished from embryonic hepatoma. For a good discussion of the several kinds of malignant hepatic tumours in infancy, consult Wells's paper (1940). The tumour in a girl aged 9 reported by Kilfoy and Terry is a good example of a hepatic carcinoma probably not of embryonic origin, and the same applies to many of the other cases tabulated by them. It must be admitted,

however, that distinction between truly embryonic liver cell tumours and ordinary hepatomas arising in childhood may be neither histologically, possible nor theoretically valid, they may differ only in their time of origin. In view of this, it would be pointless to attempt analysis of the age incidence and other properties of hepatoblastomas. Suffice it to recognize that there *are* tumours of liver tissue of unquestionable embryonic qualities. It will be helpful to review briefly a few typical examples.

(1) Some examples of embryonic hepatic tumours

Nissel described a large tumour of the liver of a new born infant, consisting of epithelial tissue of trabecular arrangement accompanied by much spindle-celled mesenchymal tissue containing areas of cartilage and bone. Nissel supposed the tumour to have arisen from a focus of embryonic liver tissue containing both epithelium and connective tissue and the bone and cartilage to have developed from the latter by metaplasia.

In Sheehan's case, a large tumour of the right lobe in a girl aged 6 years was associated with congenital cystic disease of the organ and the tumour had massively invaded the common bile duct and had produced several discrete metastases in the liver itself. Microscopical examination showed the cystic bile ducts to contain papillary growths, and the tumour to consist mainly of non-epithelial tissues derived from the abnormal connective tissue of these papillary formations. These were myxomatous, fibromatous and rhabdomyomatous, but with all transitional forms. Early papillary growths in the cysts showed mesenchymal changes similar to those in the main tumour, including the development of mucoid tissue and of striated fibres. Sheehan's views regarding the histogenesis of the tumour are worth citing. In view of the tissue balance during early foetal life between the hypoblastic liver bud and the mesenchyme into which it grows we may expect a maldevelopment of the one to lead to a reciprocal maldevelopment of the other. The later supervention of active growth on the part of the hypoblastic cells will then lead to the formation of carcinoma or hepatoma, and on the part of the mesenchymal cells to sarcoma of various kinds. The participation of both divisions leads to the true mixed tumours. In the present case the hypoblast has not developed to hepatoma and remains benign as the epithelium of the cysts while the embryonic connective tissue cells have undergone the malignant development.

In a female infant 11 months old with marked overgrowth of the left side of the body, Roth found a large hepatic tumour composed of hepatoma like epithelial growth, foci of cornifying squamous epithelium and young mesenchymal tissue containing patches of cartilage and bone.

Webster described three specimens of malignant hepatoma from male infants aged 6, 4 and 18 months. The first tumour contained much carcinomatous tissue of diverse arrangement but resembling hepatic tissue, much osteoid tissue with patchy calcification and sarcoma like areas of cellular connective tissue and Webster regarded it as an hepatic analogue of Wilms's tumour. The tumours in Webster's second and third cases consisted of hepatoma like epithelial growth only and showed no noteworthy stromal changes.

In the following personally studied case also the tumour was a simple embryonic hepatoma without any heterotopic tissues.

(a) Invasion of veins

This is sometimes conspicuous, and is of course an important factor in prognosis. Examples of extensive growth within the renal veins and inferior vena cava and even into the heart are recorded by Merkel, Engelken, Muus, Rosenstein, Loughnane and Dew. In Dew's case, the left sided renal tumour extended to the cord and testis within the spermatic veins.

(b) Metastases

These are most frequent in the lungs, but may occur also in liver, bones, lymph nodes and peritoneum. Noteworthy reports include those of Merkel, Engelken, Hedren (Case 5), Loughnane, Fraser, Wollstein, Kretschmer and Hibbs, Grewal, and Mintz, the last two writers particularly describing metastases in bones. In many cases the structure of the metastases has been as complex as that of the primary tumour, showing the immaturity and multipotentiality of the neoplastic blastema cells transported.

(6) Embryonic renal tumours in animals

Tumours undoubtedly comparable with the embryonic tumours of the human kidney occur in the pig (Feldman 1932, Chapter XXI) ox (Feldman Fig 188), sheep (Feldman, 1933) rabbit and hare (Bell and Henrici, Scott, Polson, Eisler) rat (Bullock and Curtis, Ratcliffe) and fowl (McKenney, Feldman and Olson). Nephroblastomas are the commonest of all tumours in pigs, and are also relatively frequent in chickens. Most of the affected animals are young. As in humans, most of the tumours are unilateral and solitary, but bilateral growths sometimes occur as in 8 of Feldman's 46 tumours of swine and in the fowl reported by Feldman and Olson. In structure the growths generally resemble their human counterparts showing a mixture of undifferentiated tissue and differentiating tubular, glomerular and connective tissues (Many excellent figures by Feldman). Conspicuous squamous change, as in Feldman and Olson's specimen, is infrequent, and striated muscle fibres, as in one of Bullock and Curtis's rats, have rarely been seen. Metastasis has been observed in the pig, ox and sheep, rarely in the fowl, and not at all in the rodents, in which the tumours appear to be relatively benign.

EMBRYONIC TUMOURS OF THE LIVER HEPATOBLASTOMA

Tumours clearly comparable with the embryonic tumours of the kidney occasionally arise in the liver. They occur in the foetus or young infant and consist of embryonic liver tissue, sometimes accompanied by heterotopic tissues also. In considering these tumours three sources of confusion are to be avoided, namely, (i) metastatic neuroblastoma must not be mistaken for a primary liver tumour, (ii) congenital angiomas must be distinguished from hepatoblastoma, and (iii) primary carcinoma of adult type occurring in childhood or youth should be distinguished from embryonic hepatoma. For a good discussion of the several kinds of malignant hepatic tumours in infancy, consult Wells's paper (1940). The tumour in a girl aged 9 reported by Kilfoy and Terry is a good example of a hepatic carcinoma probably not of embryonic origin and the same applies to many of the other cases tabulated by them. It must be admitted,

however, that distinction between truly embryonic liver cell tumours and ordinary hepatomas arising in childhood may be neither histologically, possible nor theoretically valid, they may differ only in their time of origin. In view of this, it would be pointless to attempt analysis of the age incidence and other properties of hepatoblastomas. Suffice it to recognize that there *are* tumours of liver tissue of unquestionable embryonic qualities. It will be helpful to review briefly a few typical examples.

(1) Some examples of embryonic hepatic tumours

Nissel described a large tumour of the liver of a new born infant, consisting of epithelial tissue of trabecular arrangement accompanied by much spindle celled mesenchymal tissue containing areas of cartilage and bone. Nissel supposed the tumour to have arisen from a focus of embryonic liver tissue containing both epithelium and connective tissue, and the bone and cartilage to have developed from the latter by metaplasia.

In Sheehan's case, a large tumour of the right lobe in a girl aged 6 years was associated with congenital cystic disease of the organ and the tumour had massively invaded the common bile duct and had produced several discrete metastases in the liver itself. Microscopical examination showed the cystic bile ducts to contain papillary growths and the tumour to consist mainly of non epithelial tissues derived from the abnormal connective tissue of these papillary formations. These were myxomatous, fibromatous and rhabdomyomatous but with all transitional forms. Early papillary growths in the cysts showed mesenchymal changes similar to those in the main tumour including the development of mucoid tissue and of striated fibres. Sheehan's views regarding the histogenesis of the tumour are worth citing. In view of the tissue balance during early foetal life between the hypoblastic liver bud and the mesenchyme into which it grows we may expect a maldevelopment of the one to lead to a reciprocal maldevelopment of the other. The later supervention of active growth on the part of the hypoblastic cells will then lead to the formation of carcinoma or hepatoma, and on the part of the mesenchymal cells to sarcoma of various kinds. The participation of both divisions leads to the true mixed tumours. In the present case the hypoblast has not developed to hepatoma and remains benign as the epithelium of the cysts, while the embryonic connective tissue cells have undergone the malignant development.

In a female infant 11 months old with marked overgrowth of the left side of the body Roth found a large hepatic tumour composed of hepatoma like epithelial growth, foci of cornifying squamous epithelium and young mesenchymal tissue containing patches of cartilage and bone.

Webster described three specimens of malignant hepatoma from male infants aged 6, 4 and 18 months. The first tumour contained much carcinomatous tissue of diverse arrangement but resembling hepatic tissue, much osteoid tissue with patchy calcification and sarcoma like areas of cellular connective tissue and Webster regarded it as 'an hepatic analogue of Wilms's tumour'. The tumours in Webster's second and third cases consisted of hepatoma like epithelial growth only and showed no noteworthy stromal changes.

In the following personally studied case also the tumour was a simple embryonic hepatoma without any heterotopic tissues.

and young children (e.g. many of the congenital sarcomas tabulated by Wells) are of this nature, that is, they have arisen from and continue to reproduce undifferentiated mesenchyme, they are embryonic mesenchymomas. Since adult mesenchymal tissues may contain plastic indifferent cells or may revert to embryonic condition when they multiply (see Chapter 41), sharp distinction between primarily embryonic mesenchymomas on the one hand and mesenchymomas with reversionary embryonic qualities in adults on the other, is probably impossible. Yet, for theoretical reasons set forth in the following paragraphs, we should attempt to make the distinction as far as possible.

GENERAL COMMENTS ON THE CAUSATION AND SIGNIFICANCE OF EMBRYONIC TUMOURS

Most of the ordinary tumours of adult life arise only after prolonged exposure of the tissues to carcinogenic chemical substances or other agents. This cannot apply to embryonic tumours: they arise during actual organogenesis from tissues still immature and some of them attain large sizes and produce metastases even during the brief span of intra uterine life. The causes of these growths must be very different from those of adult tumours; they must be sought in disturbed embryonic chemistry—the chemistry of the organisers, those substances which are responsible for the mutual inductive effects of one tissue on another during organogenesis and differentiation. Yet, when discovered, the chemistry of these disturbances may well shed light on the fundamental problem of tumour growth, the very nature of the irreversible change in the tumour cells. For this reason, the embryonic tumours and the kindred teratomas are of peculiar interest and merit the closest study.

The embryonic tumours are simultaneously tumours and malformations. In Chapter 1 it was pointed out that not all malformations are congenital, but that errors of development may and do arise during post-natal life, in tissues which are still immature, such as the bones, teeth and gonads. This applies also to the embryonic tumours; theoretically the time range of possible origin of an embryonic tumour of a particular kind is the whole period—post natal as well as foetal—during which the parent tissue remains immature and we should expect tumours originating early in the embryonic or foetal period to be less mature and more malignant than those arising later. The age incidence of the several kinds of embryonic tumours accords well with this theoretical concept. Thus immature neuroblastic tissue is scanty in the sympathetic system soon after birth: most neuroblastomas make their clinical appearance within the first 3 or 4 years of life, and the earliest appearing are on the average the most embryonic. Retinal differentiation is complete at or soon after birth: two thirds of retinoblastomas have become clinically apparent before the age of 3. Cerebellar differentiation is nearly complete by the end of the first year of post natal life, but some proliferation continues at the rhombic lip much later than this: cerebellar medulloblastomas arise chiefly in young children but occur also in older children and adolescents. Formation of renal tissue from the immature nephrogenic cap is complete soon after birth: the majority of nephroblastomas are discovered before the age of 3 years. We cannot put a terminal date to the formation of new liver tissue for this tissue has great powers of regeneration.

however, that distinction between truly embryonic liver-cell tumours and ordinary hepatomas arising in childhood may be neither histologically, possible nor theoretically valid—they may differ only in their time of origin. In view of this, it would be pointless to attempt analysis of the age incidence and other properties of hepatoblastomas. Suffice it to recognize that there are tumours of liver tissue of unquestionable embryonic qualities. It will be helpful to review briefly a few typical examples.

(1) Some examples of embryonic hepatic tumours

Nissel described a large tumour of the liver of a new born infant, consisting of epithelial tissue of trabecular arrangement accompanied by much spindle celled mesenchymal tissue containing areas of cartilage and bone. Nissel supposed the tumour to have arisen from a focus of embryonic liver tissue containing both epithelium and connective tissue and the bone and cartilage to have developed from the latter by metaplasia.

In Sheehan's case a large tumour of the right lobe in a girl aged 6 years was associated with congenital cystic disease of the organ and the tumour had massively invaded the common bile duct and had produced several discrete metastases in the liver itself. Microscopical examination showed the cystic bile ducts to contain papillary growths and the tumour to consist mainly of non-epithelial tissues derived from the abnormal connective tissue of these papillary formations. These were myxomatous, fibromatous and rhabdomyomatous but with all transitional forms. Early papillary growths in the cysts showed mesenchymal changes similar to those in the main tumour, including the development of mucoid tissue and of striated fibres. Sheehan's views regarding the histogenesis of the tumour are worth citing. In view of the tissue balance during early foetal life between the hypoblastic liver bud and the mesenchyme into which it grows, we may expect maldevelopment of the one to lead to a reciprocal maldevelopment of the other. The later supervention of active growth on the part of the hypoblastic cells will then lead to the formation of carcinoma or hepatoma and on the part of the mesenchymal cells to sarcoma of various kinds. The participation of both divisions leads to the true mixed tumours. In the present case the hypoblast has not developed to hepatoma and remains benign as the epithelium of the cysts while the embryonic connective tissue cells have undergone the malignant development.

In a female infant 11 months old with marked overgrowth of the left side of the body Roth found a large hepatic tumour composed of hepatoma like epithelial growth foci of cornifying squamous epithelium and young mesenchymal tissue containing patches of cartilage and bone.

Webster described three specimens of malignant hepatoma from male infants aged 6, 4 and 18 months. The first tumour contained much carcinomatous tissue of diverse arrangement but resembling hepatic tissue, much osteoid tissue with patchy calcification and sarcoma like areas of cellular connective tissue and Webster regarded it as an hepatic analogue of Wilms's tumour. The tumours in Webster's second and third cases consisted of hepatoma like epithelial growth only, and showed no noteworthy stromal changes.

In the following personally studied case also the tumour was a simple embryonic hepatoma without any heterotopic tissues.

REFERENCES

GENERAL

- WELLS, H G (1940) Occurrence and significance of congenital malignant neoplasms
Arch Path 30 535 (A valuable review)

EMBRYONIC RENAL TUMOURS

- Bell E T and Henrici A T (1916) *J Cancer Res* 1 157
 Bosse M D (1940) *Arch Path* 30 1235
 Bullock F D and Curtis M R (1930) *J Cancer Res* 14 1
 Busse O (1899) *Virchows Arch* 157 346
 Busser F Cayla A Delon J and Corcelle J (1938) *Ann Anat path* 15, 212
 Cohnheim J (1875) *Virchows Arch* 65 64
 Delon J (1935) *Ann Anat path* 12 836
 Dew H R (1928) *Surg Gyn Obst* 46, 447
 Eberth C J (1872) *Virchows Arch* 55 518
 Eisler B (1938) *Z Krebsforsch* 48 235
 Engelken H (1899) *Beitr path Anat* 26 320
 Eve F S (1882) *Trans Path Soc Lond* 33 312
 FELDMAN, W H (1932) *Neoplasms of Domesticated Animals* Chapter XXI Philadelphia
 (Excellent microphotographs of some animal tumours)
 Feldman W H (1933) *Amer J Cancer* 17 743
 Feldman W H and Olson C (1933) *Ibid*, 19 47
 FRASER, J (1920) Adenosarcomatous tumours of the kidney *Edinb Med J* 24 372
 (Stresses the undifferentiated bipotential nature of the sarcomatous tissue)
 Foucar F H (1935) *Amer J Path* 11 753
 Grewal J S (1932) *Arch Path* 13 681
 Hamm F C (1942) *J Urol* 47 403
 Hasner R B (1928) *Arch Path* 6 240
 HEDRLN, G (1907) Zur Kenntnis der Pathologie der Mischgeschwulste der Nieren *Beitr path Anat* 40 1 (An exhaustive review of previous records)
 Herzog H (1938) *Z Krebsforsch* 48 424
 Hoisholt A W (1886) *Virchows Arch* 104 118
 Kilbane E F and Lester C W (1929) *Surg Gyn Obst* 49 710
 ARETSCHMER, H L, and HIBBS, W G (1931) Mixed tumors of the kidney in infancy and childhood *Surg Gyn Obst* 52 1 (A well illustrated account of 17 cases)
 Loughnane F M (1914) *Brit J Surg* 2 77
 Marchand F (1878) *Virchows Arch* 73 289
 Masson P (1938) *Amer J Cancer* 33 1
 McCurdy G A (1934) *J Path Bact* 39 623
 McKenney F D (1931) *Amer J Cancer* 15 122
 Merkel H (1898) *Beitr path Anat* 24 475
 Mintz E R (1934) *J Urol* 31 79
 Moore T (1943) *Brit J Surg* 30 381
 MUUS, N R (1899) Ueber die embryonalen Mischgeschwulste der Niere *Virchows Arch* 155 401 (A valuable review with sound ideas on histogenesis)
 Nicholson G W (1922) *Guy's Hosp Rep* 72 75
 NICHOLSON G W (1931) An embryonic tumour of the kidney in a foetus *J Path Bact* 34 711 (An admirable exposition of histogenesis)
 Papin E Busser F and Corcelle J (1938) *Ann Anat path* 15 645
 Polson C J (1927) *J Path Bact* 30 603
 Ratchiffe H L (1940) *Amer J Path* 16 237
 Rosenstein P (1899) *Arch klin Chir* 60 596
 Scott E (1917) *J Cancer Res* 2 367
 Sparks A J (1942) *J Urol* 47 642
 Williams D (1882) *Trans Path Soc Lond* 33 317
 Wollstein M (1927) *Arch Path* 3 1

even in the adult, but most of the clearly embryonic hepatic tumours especially those with heterotopic elements, have been found in young infants. Again as already pointed out the great powers of adult mesenchymal tissue for proliferation and aberrant redifferentiation make it difficult and perhaps unnecessary to distinguish sharply between embryonic mesenchymal tumours and those developing later.

What of certain other tissues the adult differentiation of which is not complete until long after birth especially the skeleton and teeth? Can embryonic tumours arise post nately in these? In a sense yes. The properties of multiple exostoses, ossifying ecchondromas and hereditary enchondromas, the causes of which are clearly related to developmental disturbances are in part determined by their having arisen from young growing skeletal tissues. Perhaps the causes of some of the osteogenic sarcomas and osteoclastomas of children and adolescents are to be sought more in disturbances of the chemistry of skeletal growth than in the direct application of extrinsic carcinogenic agents. Of course sarcomas of bone can be produced by radio active substances or by the experimental insertion of hydrocarbons but these causes may be false guides to knowledge of the causation of most of the bone tumours of youth for which greater understanding of calcium and phosphorus exchanges and of the enzymes and metabolism of young bone tissue may be much more relevant. Tooth tissue is immature throughout childhood and early adolescence, and it is significant that in the majority of cases tumours of the paradental residues the adamantinomas appear during adolescence or early adult life. It seems unlikely that these residues can be subjected to extrinsic carcinogens and much more probable that the causes of neoplasia in them may be disturbances in their own metabolism and growth during their formation. In this sense the adamantinomas of the jaw may be looked upon as embryonic tumours, i.e. as tumours arising in a still immature tissue and evoked by factors disturbing the growth and maturation of the tissue. The same applies to the 'adamantinomas' of the parapatitular residues which also arise during childhood in a high proportion of cases.

The great significance of the embryonic tumours is that they show that carcinogenesis does not always imply the application of identifiable carcinogenic substances from without but may result also from disturbances of metabolism and maturation of growing tissues. Of course these disturbances are themselves caused no doubt by external factors but these factors need not themselves be carcinogenic in the ordinary sense. They may merely consist in certain combinations of circumstances—excess or defect of particular mineral or nutritive substances vitamins hormones oxygen etc—which so impede or deviate normal growth and differentiation that neoplasia results. It is possible that the disturbed metabolism itself results in the formation in the developing tissues of carcinogenic chemical substances perhaps of a sterol nature which might be extracted and identified. All this of course is speculative but we are constrained to such speculations by the peculiar phenomenon of embryonic neoplasia which clearly demands very different concepts regarding causation from those which occupational and experimental studies have engendered.

CHAPTER 61

THE TERATOMATA

INTRODUCTION

"FAR from adopting the time honoured method of human teratology of taking the lightest fancies of our predecessors for gospel (provided they have acquired substance and reality in print), we must lay down rules for our guidance, adhere to them rigidly and ruthlessly refuse to entertain all nonconforming utterances of authority. And we cannot do better than allow ourselves to be guided by the Cartesian axiom, that *we are not bound to accept—indeed, that we are properly bound not to accept—a proposition that is not perfectly clear and distinct* (Nicholson, 1935 Study No XVI, p 10)

In view of the arresting heterotopic structures seen in many teratomas, it is not surprising that study of these growths more than any other group of tumours has been confused by fanciful hypotheses. False identification of bones, organs and whole parts of the human body without proper dissection or microscopical study, has abounded and at least a dozen different histogenetic hypotheses, based on no more than their authors' imaginations have been advanced and endlessly debated. Some of the main hypotheses will be discussed at the end of this chapter after the structure and behaviour of the tumours have been described.

It would be a useless task to attempt a critical outline of even the chief of the huge number of papers on teratomas. Amongst the best reviewers of those of last century are Ahlfeld (1875), Wilms (1896), Askanazy (1907) and Ohkubo (1908). Of the more recent contributors to the subject by far the most important for his critical scientific approach is Nicholson (1929, 1930, 1934, 1935 and 1937), whose thoroughness of description I have tried to emulate in my own studies (1935, 1936 and 1937).

DEFINITION AND CLASSIFICATION

(1) Definition

A teratoma is a true tumour or neoplasm composed of multiple tissues of kinds foreign to the part in which it arises.

It is a *true tumour* i.e. it displays some degree of progressive uncoordinated growth and is not merely a quiescent malformation. Teratologists have often confused teratomas and malformations devoid of neoplastic qualities. It is true that some highly differentiated teratomas, e.g. some of the so-called "dermoid cysts", come to consist of quiescent tissues of mature adult type but this applies to some individual members of almost any group of tumours. Some "dermoid cysts" though the most benign members of the teratoma family, display progressive growth and these cannot be sharply separated from polycystic and solid teratomas of more active growth, less complete maturation of the tissues, and potential or actual malignancy. Non neoplastic malformations lack these

EMBRYONIC HEPATIC TUMOURS

- Kilfoy E J and Terry M C (1929) *Surg Gyn Obst*, 48 751
Nissel W (1928) *Virchows Arch*, 269 446
Roth F (1938) *Frankfurt Z Path* 52 163
Sheehan H L (1930) *J Path Bact* 33 251
Webster R (1938) *Med J Austral* ii 381

Even a mixed tumour arising during early stages of development is not a teratoma if it contains only regionally indigenous tissues, e.g. the compound salivary glandular and lipomatous tumour of Case I, Chapter 42. So also, we should distinguish between teratomas and embryonic tumours of particular viscera such as nephroblastoma and hepatoblastoma, even though some of the latter are "mixed" tumours in that they show aberrant differentiation of some of their embryonic tissues. Thus Wilms's tumours of the kidney, even though they may contain striated muscle fibres, cartilage or squamous epithelium, are still clearly nephroblastomas derived from and composed of embryonic renal tissue. The heterotopic tissues in these tumours display the dormant potencies for aberrant differentiation inherent in embryonic renal tissue, comparable with the metaplastic potencies of adult tissues, but the tumours do not produce completely exotic tissues, such as salivary, respiratory, dental or neural tissues, all of which are common in true teratomas. However, in common with teratomas, the mixed embryonic tumours of particular organs have their origins in developmental disturbances at early stages and a capacity greater than that of matured tissues for diverse differentiation. They differ from teratomas in their more restricted potencies, a restriction clearly related to the regional restriction of potencies within the particular organs or localities from which they arise.

(2) Classification

All teratomas constitute a single class and sub-divisions of the class on either structural or behaviouristic grounds are arbitrary. This principle has been repeatedly enunciated by almost all serious students of the subject including Wilms, Askanazy, Ohkubo, Nicholson and myself.

Structural sub-division into cystic and solid growths into monodermal, bidermal and tridermal ones, according to the number of 'germ layers' represented by the tissues discovered in them, and into those composed of mature adult tissues and those containing embryonic tissue, are all quite artificial. Predominantly cystic growths contain plenty of solid tissues, predominantly solid growths almost always contain plentiful small cysts. The number of tissues discovered and whether these represent derivatives of one, two or three of the germ layers of normal ontogeny depend mainly on how thorough the search has been. Full examination will show that almost all teratomas are "tridermal" for they almost all contain skin, teeth or nervous tissue ('ectoderm'), respiratory or alimentary epithelia ('endoderm'), and they all contain connective and vascular tissue at least ('mesoderm'). But, in any case, the three germ layers of normal development have no real relevance in the structure of teratomas for these show no evidence whatever of orderly delamination. Division of teratomas into those composed wholly of mature tissues and those containing embryonic tissues is of practical value, for the former are usually benign and the latter malignant, yet the distinction is arbitrary, since all degrees of maturity of the tissues are encountered and since mixtures of adult and embryonic tissues in all proportions occur.

The behaviouristic distinction between "benign" and "malignant" teratomas can be made in most cases. But, as with other classes of tumours, benign and malignant are relative terms, and borderline tumours occur. Structure

qualities. Masses of pancreatic and gastric tissue in the walls of Meckel's diverticula, branchial cysts, enterocysts, developmental dermoid cysts beneath the skin or in the cranial cavity or spinal canal—all of these are malformations containing multiple heterotopic tissues, but they are not teratomas, nor related to them. Also to be distinguished from teratomas are double monsters, acardiac amorphous and other forms of suppressed twins, whether externally attached or included (if this ever happens) and duplications of main parts, these also lack neoplastic attributes. It is I believe, a mistake to suppose that a gentle series of gradations exists between double monsters and malformed twins on the one hand and teratomas on the other—a mistake widely promulgated because of a prevalent view that teratomas *are* included monsters or malformed twins. The sooner this misconception is abandoned the better. There may be occasional specimens the nature of which it is difficult to decide whether teratomatous or monstrous formations e.g. some of the epignathi. But I personally have yet to see such a specimen. none of the many teratomas and malformations which I have examined properly has occasioned any such difficulty. Moreover, the descriptions of many of the supposed examples of borderline or transitional lesions between teratomas and monsters show how incompletely the specimens were examined.

Teratomas contain multiple tissues. The more thoroughly they are examined, the greater the variety of tissues found in them. The notion that some of them contain only one kind of tissue or tissues of 'only one germ layer' is almost always a confession of inadequate examination. Even in the simplest 'dermoid cysts', proper topographical study will rarely fail to reveal in addition to skin and its appendages and adipose tissue other kinds of tissues also—neural skeletal dental respiratory or alimentary. This is the place to insist—what indeed should be self-evident—that a teratoma has not been adequately studied until it has been thoroughly dissected and all relevant structures examined microscopically or until it has been topographically reconstructed from serial sections in the case of small tumours or, in the case of large tumours from thin serial slabs, as described in my papers. The only teratomas which consist of only one kind of tissue are those rare highly malignant growths composed of completely undifferentiated embryonic tissue the differential potencies of which are of course not manifested as in the recurrent growth in the case providing my specimens Nos. XVIII and XIX (1937). How unwise it is to regard as 'teratomatous' tumours devoid of demonstrably multiple tissues is seen in Ewing's hypothesis of the nature of seminomas. this has been dealt with in Chapter 33.

Teratomas contain tissues of kinds foreign to the part. There are many malformations and some tumours composed of and derived from multiple tissues indigenous to the region but these are not teratomas. A mammary fibroadenoma though composed of two distinct neoplastic tissues is not a teratoma because these tissues are both mammary tissues. It is not even a teratoma when its fibroblastic component undergoes cartilaginous and bony changes, for these are but metaplasias often displayed by fibroblastic tissues under abnormal conditions. So also mixed tumours of the adult thyroid uterus or other parts should be distinguished from teratomas because their tissues represent and are derived from those of the region even though they may assume metaplastic disguises.

(1) Teratomas of the ovaries

(a) Type

These the most familiar of all teratomas need no detailed description, many typical examples are given in the papers already cited. Most of them are of the benign highly differentiated, cystic variety—so-called 'dermoid cysts' (Figs 464-465). This term however, is unfortunate for two reasons—(a) the same name is applied (and correctly so) to lesions unrelated to teratomas, the sequestration dermoid cysts of the skin, cranial cavity and other parts, and (b) to call any teratoma a 'dermoid cyst' is to give always an incomplete and often an erroneous

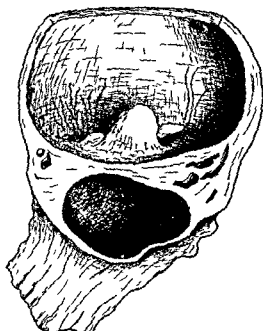


FIG 464—Drawing of benign teratoma of ovary containing two large and several small cysts with a skin-covered eminence carrying a tooth in the largest cavity. The divided mesovarium is below. (Hillis 1935 Case IX) (Natural size)

idea of its structure. Skin lined cavities are frequent components of teratoma, in a 'dermoid cyst' one or more of these cavities has become distended by accumulating sebum to form the bulkiest part of the growth, the other components of which now form a relatively small solid or cystic eminence projecting into the sebum filled cavity. This eminence always contains tissues other than skin of as great a variety as those seen in the solid and polycystic teratomas. Frequently, too the main cavity is lined partly by skin and partly by other tissues, respiratory, alimentary or nervous and it contains not only sebum but also mucus and other secretions of these tissues. In some tumours the main cavity is lined entirely by one of these tissues and not at all by skin, e.g. in my Case XXI (1937) it was lined by nervous tissue and choroid plexus and its contents was clear fluid undoubtedly cerebrospinal fluid. In a small minority of cases ovarian teratomas are solid and malignant as in my Case XV (1937) and Webster's case (1938).

is usually, but not always a safe guide in prognosis, e.g. the bilateral tumours XVIII and XIX of my 1937 paper had a well differentiated "benign" structure yet highly malignant recurrent growth rapidly developed while tumour XVII contained active tissues of doubtful maturity and innocence but the patient remained well several years after removal of the growth. However tumours which contain clearly embryonic components are usually clinically malignant.

THE SITES OF TERATOMAS

The main sites of teratomas are in order of frequency, the ovaries the testes, retroperitoneal region the anterior mediastinum, pre sacral and coccygeal region and the base of the skull. Rarer sites include the pineal gland brain and neck. Teratomas rarely, if ever, arise in the face posterior mediastinum thoracic and abdominal viscera (other than the gonads) thoracic and abdominal walls and the extremities. The few 'teratomas' which have been reported in these situations are of dubious nature, some at least of them have certainly been imperfect twin inclusions or other non neoplastic malformations while others have been non teratomatous mixed tumours (see breast, thyroid uterus bladder).

The following table shows the number and situations of the teratomas in 82 cases which I have studied, and gives references to the 42 cases reported.

Site	No of cases	Remarks	References to reports
Ovary - - -	50	Benign 42 cases benign but with supervening carcinoma 5 cases malignant teratoma 3 cases (Bilateral tumours in 6 cases)	(a) Willis 1935 (b) 1936 (c) 1937 (d) 1939 (e) Stewart Willis and De Saram 1939 (f) Willis 1942
			21 cases
Testis - - -	19	All malignant (Associated with seminoma in 4 cases)	(a) Willis 1935 6 cases (b) Chapter 33 Cases III-VI
Epididymis - -	2	Both benign (Associated with seminoma in 1 case)	(a) Case I below (b) Chapter 33 Case VII
Retroperitoneal -	3	All benign	(a) Willis 1935 (b) Gale and Willis 1944
Presacral - -	2	Both benign	Willis 1935 (1 case)
Anterior mediastinal	3	All benign	Willis 1935 (2 cases)
Intra pericardial -	1	Benign	Willis 1946
Brain - - -	2	Both malignant	Cases II and III below

(c) Age

The mean age of 48 cases in my series was 33 years, the three youngest patients were 8, 11, and 12, the largest number of cases (18) were in the third decade, 26 (i.e. more than one half), were under 30, the three oldest patients were 68, 67 and 63 and all three of these had carcinomas supervening in previously benign cystic teratomas (Cases IV, VI and VII below). Two other patients (Cases V and VIII below) who also had supervening carcinomas, were aged 48 and 40.

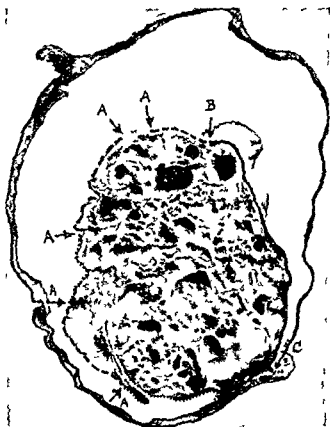


FIG. 466—Slice of an ovarian teratoma composed of a solid and polycystic mass projecting into a large thin walled cyst. Microscopically this mass was clothed by nervous tissue (continuous line) epidermis (interrupted line) and respiratory epithelium (dotted line) with abrupt transitions at A, B and C (see Fig. 484) (Willis, 1937, No. XVII) (Natural size).

In sharp contrast with these cases of supervening malignancy of single tissues practically all of the malignant solid or polycystic teratomas occur in childhood or adolescence. Huge dermoid cysts (see below) are always from middle aged or old subjects. Since most ovarian teratomas are obviously old tumours when they are first discovered—usually either because of their size or because of torsion or other complications—it is clear that these growths begin in very early life. Doran gave references to some of the first recorded cases of surgical removal of ovarian teratomas in young children of ages 1 year and 8 months, 2 years, 2 years and 11 months and of 4, 7 and 8 years. Shattock described a large tumour from a child aged 2½ and Wakeley (1933) reported cases 8, 9 and 9 years of age.

(d) Familial incidence

This has only occasionally been noted and is probably no more than fortuitous

A tumour of borderline type with a large solid or polycystic mass of well differentiated but not fully mature tissues projecting into the main cyst is depicted in Fig 466

(b) Site

It has often been noted that ovarian teratomas occur with greater frequency in the right than in the left ovary and this also has been my experience Of 50 cases which I have studied 20 had right sided tumours 8 left sided in 16 the side was not stated and 6 had bilateral tumours In 7 of 31 cases studied by Doran (1884) the tumours were bilateral Although it is quite possible that multiple separate teratomas may sometimes develop in one ovary proof of multiplicity

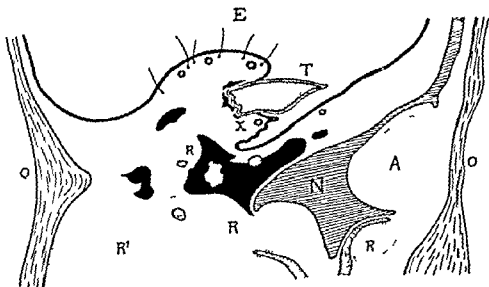


FIG 465 —Diagram of tissues found in vertical section of tumour shown in Fig 464 Heavy black line is skin with hairs and glands T = tooth X = position of paradental residues N = central nervous tissue R = cysts lined by respiratory epithelium A = cyst lined by alimentary epithelium Black areas bone close stipple cartilage wide stipple adipose and connective tissue O = layer of ovarian tissue ($\times 2$)

in so small an organ is difficult to obtain The supposedly multiple teratomas described and reviewed by Novak may equally well have been merely multiple cysts of single teratomas Aschheim described a case of bilateral ovarian teratomas accompanied by a separate intra tubal teratoma

It is necessary to mention here in order to dismiss the claim of several workers to have seen the origin of a teratoma from the lining of an ovarian follicle Thus, Thornton (1874) saw a teratoma associated with some supposedly simple Graafian cysts one of which contained a patch of hairy skin but there is nothing in Thornton's account to show that these simple cysts were not parts of the teratoma Gardner (1938) saw a small teratoma in what he supposed to be an atretic follicle lined by granulosa cells but his description and figures suggest that his granulosa cells may well have been altered stratified epithelium lining a teratomatous cyst

(2) Teratomas of the testes

(a) Type

Most teratomas of the testis are solid malignant growths when first discovered, benign cystic growths form a small minority. Save for this reversal of the relative frequency of benign and malignant growths, the testicular tumours are in general similar to their ovarian counterparts, and, as in the ovary, some tumours show mixtures of well differentiated tissues and malignant embryonic ones.

(b) Site

Most series show a predominance of right sided growths, e.g. 43 right-sided to 23 left sided in Ohkubo's review 11 to 5 in my series. With rare exceptions teratomas of the male reproductive organs are intra testicular, teratomas of the epididymis are very rare. A formerly prevalent view, promulgated by Bland Sutton, that the usual origin of testicular teratomas was from the "paradidymis" was certainly erroneous. Teratomas of the epididymis are exemplified in Case VII of Chapter 33 and in the following case.

Case I—A man aged 28 had an inguinal hernia and had also noticed for 5 years a firm mass attached to the descended but small testis on the same side. Mr A. F. MacLure, of Melbourne, repaired the hernia and removed the testis with the attached tumour which was entirely extra testicular and occupied the upper part of the epididymis. The tumour was a well defined mass 2 centimetres in main diameter containing multiple cysts. Microscopically it was found to contain cavities lined by ciliated pseudo stratified epithelium, columnar goblet celled epithelium, or simple columnar or cuboidal epithelium associated with glands resembling Brunner's glands, a few small islands of pancreatic tissue, much smooth muscle and occasional foci of cartilage.

Bilateral teratomas are rare but it is possible that a patient who has been found to have a teratoma in one testis is more likely than a normal man to have one in the other testis, though this enhanced risk has not been proved conclusively as it has for seminoma (see Chapter 33). There is, however, no doubt that the imperfectly descended testis is more liable than the normal organ to teratoma, as it is to seminoma, and that this applies also to the intra abdominal testes of pseudo hermaphrodites (Carmichael and Oldfield). It has been suggested by several workers that some retroperitoneal teratomas may arise from supernumerary testes which have occasionally been found in this region (Staemmler).

(c) Age

As already noted in Chapter 33, the mean age of patients with teratomas of the testis is about 30. The benign cystic growths are discovered in much younger patients than the commoner malignant ones, most of them being found in children and some of them being noticed at birth. Wilms reviewed the older records and concluded that nearly all "dermoids" of the testis were probably congenital. Of 31 cystic teratomas reviewed by Ohkubo 25 were discovered before the age of 25 and 16 before the age of 8. Examples of benign teratomas found in infancy, and certainly or probably congenital include those of Geinitz, Parker, Muller, Horst and Aboukhalil and Wakeley.

Koltonski saw a mother and daughter both with ovarian teratomas, and Sippel three sisters

(e) *Associated ovarian lesions*

The association of ovarian cysts or cystadenomas with teratomas as described by Doran Stewart and Eglinton and many others is probably only fortuitous since the former are very common and the latter far from rare. In only 5 of my 50 cases of teratoma were there associated ovarian lesions, these were simple cysts in 3 cases, pseudomucinous cystadenoma in 1 case and surface fibro papillary growths in 1 case all 5 patients were adults. Teratomatous cysts lined by epithelium of intestinal type have probably been mistaken for pseudomucinous ovarian cysts. Except for a superficial resemblance there is no evidence to support a view at one time popular and still supported by Novak, that pseudomucinous cysts consist of teratomatous intestinal tissue. McCrea described a teratoma possibly of ovarian origin in a male hermaphrodite aged 31.

(f) *Size and contents*

Huge sizes may be attained usually by the accumulation of sebum in benign cystic growths. The contents of huge cysts sometimes form a multitude of spherical firm butter balls doubtless from mechanical agitation. Thornton (1876) described a patient aged 59 from whom 86 pints of sebaceous fluid were removed by tapping and from whom a similar amount had been removed 9 years earlier. Bland Sutton (1922) in his Fig 298 depicted a dermoid cyst containing 3 930 sebum balls. The two largest tumours in my series were (i) a unilocular dermoid lined by skin weighing 8½ pounds of which 7½ pounds consisted of sebaceous contents removed surgically from a woman aged 55 and (ii) a bilocular dermoid removed surgically from a woman aged 57 lined by skin and containing teeth and 2 gallons of sebaceous fluid in which were suspended 1 800 butter balls each about 1.5 centimetres in diameter and a few larger hair balls.

(g) *Secondary changes*

Secondary changes of clinical importance in teratomas include torsion rupture into the peritoneal cavity perforation or extension into rectum vagina or bladder infection and detachment from the ovary and implantation in other parts of the abdominal cavity (Doran Lexter Williams Mayer Ottow James Schauburger). It is significant that as Williams pointed out practically all cases reported as having intra pelvic or rectal teratomas or dermoids have been females. Port's was probably the earliest English account (1880) of a rectal dermoid removed from a girl aged 16. An early account of an unusually mobile ovarian dermoid with a long pedicle was that of Griffiths (1877) the tumour was first noticed at the age of 4 and was removed 8 years later. A clinically unimportant but frequent change in cystic teratomas is desquamation of parts of the lining epithelium and the formation of reactive tissue with many phagocytic foam cells and giant cells as described by Stewart. Patchy calcification of the degenerated wall may ensue. Thomson saw asthmatic reaction in teratomatous bronchial tissues. Carcinomatous change in benign cystic teratomas has already been referred to and is described later.

described a retroperitoneal teratoma which extended laterally and posteriorly deep to the spinal muscles and caused a swelling in the back. Retroperitoneal teratomas of the lower lumbar or ilio-pelvic region, like my Case XI (1935), are very rare.

(c) Age

The early age of appearance of most retroperitoneal teratomas is exemplified by the following cases: in Hosmer's case and in my Case X (1935), abdominal swelling had been noticed at birth; in Nicholson's case the large tumour came from an infant 4 months old; in my Case XI (1935) the huge tumour (Fig. 467) was removed at the age of 9 months; Schonholzer's and Penberthy and Brownson's patients were 2 years old; in Lexer's case a girl aged 11 was known to have had a large tumour for several years; in the case reported by Gale and myself the large tumour, consisting of fully mature quiescent tissues and with every sign of being coeval with the patient, was discovered during routine examination of a girl aged 13; and Fuller and Jagger's patient, aged 19, also had a large 'adult' tumour clearly of long standing. These findings point clearly to the congenital nature of this group of teratomas.

(d) Sex

Females appear to outnumber males, e.g. the cases just cited comprise 7 females and 3 males.

(4) Mediastinal teratomas

(a) Type

With few exceptions these are of the benign cystic variety. Reports of malignant tumours include those of Virchow (1871), Ritchie, Ceelen, Jacobs, Kantrowitz, and Houghton, who reviewed records of 25 malignant tumours. The malignancy has usually been interpreted as adenocarcinomatous or 'chorion epitheliomatous' change, but in some cases it is total, yielding complex metastases, as in Houghton's case.

(b) Site

Hedblom's useful review of nearly 200 cases showed that, almost without exception, intra-thoracic teratomas occupy the anterior mediastinum. Recently (1946) I reported a case and reviewed 4 others in which the tumours were closely connected with the great vessels at the base of the heart and projected into the pericardial cavity (Fig. 468). Posterior mediastinal teratomas are almost unknown.

(c) Age

These growths have been discovered at all periods of life, from infancy to old age. However, in more than two-thirds of the cases reviewed by Hedblom the patients were less than 30 years old. The malignant tumours mentioned above were from men aged 23, 24, 33, 27, 22 and 22 respectively, and the mean age of

(d) Associated testicular lesions

Incomplete descent and pseudo hermaphroditism have already been referred to, and in Chapter 33 the association of teratoma and seminoma is discussed

*(3) Retroperitoneal, mesenteric and mesocolic teratomas**(a) Type*

Most teratomas in these situations are benign cystic growths which attract attention in childhood by their size or pressure effects (Figs 467-475 and 477-479). Other tumours are solid malignant growths sometimes of "chorion-epitheliomatous" type: these usually manifest themselves in early adult life. As Prym (1925 and 1927) insisted, care must be taken not to mistake retroperitoneal



FIG 467 —Diagram of structure of a slice of large retroperitoneal teratoma from a female infant 9 months old. Central nervous tissue hatched; choroid plexus cavities marked C; alimentary and respiratory cavities and glands finely stippled and marked A and R; skin cavities stippled and marked S; bone and cartilage black and main masses of bone marked B; X = main cyst cavity (which contained 40 ounces of clear fluid); wide stipple denotes adipose tissue (Billis 1935 Case 17) (Slightly reduced)

metastases of small testicular teratomas for primary growths: and no malignant retroperitoneal tumour should be accepted as primary until the testes have been thoroughly examined. But cases like those of Fenster show that primary malignant retroperitoneal teratomas, unassociated with testicular disease, do occur.

(b) Site

Most of the tumours arise high up in the retroperitoneal region close to the superior mesenteric artery, coeliac artery, pancreas and kidneys. A tumour described by Nicholson (1929) was intimately attached to the upper pole of the left kidney and derived its blood supply from the left renal and upper lumbar arteries. The tumour which Gale and I reported (Figs 477-479) lay high up behind the pancreas. Some tumours arising at the same level extend forward to occupy the root of the mesentery or mesocolon (Lever, Schönholzer) or even to lie in the distal parts of the mesentery (Penberthy and Brownson). Fuller and Jagger

by mediastinitis, pneumonia empyema or perforation into trachea or bronchi. In 26 of the cases reviewed by Hedblom hair had been coughed up. Pressure on the heart or great vessels accounts for the early ages at which intra pericardial growths cause symptoms.

(5) Pre sacral and coccygeal teratomas

(a) Type

Most of these tumours are benign and cystic, and many of them contain highly organized structures such as loops of bowel, digits or other parts of limbs (see below). Some of them however, are, or become malignant. This usually appears to result from supervening adenocarcinoma, less often squamous cell carcinoma in one of the epithelial components of the growth rather than from malignancy *in toto*. Malignancy is seen even in infancy, as in the tumours with papillary adenocarcinoma described by Fletcher and Waring, Pandalar *et al*, Stewart *et al* and Lisco. Or it may supervene in previously benign tumours of long duration in adults as in the cases of Pringle and Fuss.

(b) Site

Most of the tumours project prominently externally. Their origin is clearly from the immediately pre sacral or pre coccygeal tissues. They are often attached to the anterior surfaces of the lower sacral or coccygeal vertebrae but in most cases these bones are intact. Only occasionally does the bulk of the tumour occupy the pelvis or project upwards into the abdomen, such tumours show that the retroperitoneal group and the sacrococcygeal group of teratomas differ only in level.

(c) Age

With rare exceptions sacrococcygeal teratomas are already prominent, many of them bulky at birth. There is therefore no doubt that they arise at an early period of embryonic development.

(d) Sex

As with the retroperitoneal group there appears to be a decided preponderance of females (Hausmann and Berne, Williams, 1935).

(6) Epignathus and teratomas of the skull base

Ahlfeld (1875) gave an excellent review of the earlier reports of epignathus, from which he concluded that 'Often neither the illustrations nor the reports enable us to decide whether the descriptions had a scientific basis or not. As to the contents of the tumours here also writers have often indulged in fantasy — comments still appropriate for many more recent descriptions.

(a) Type

Epignathus and basal cranial teratomas consist of well differentiated tissues, often including highly organized structures, such as parts of limbs. Malignant

the 25 cases with malignant tumours reviewed by Houghton was 27 Of the 5 intra pericardial tumours referred to in my 1946 paper, 3 were known to be congenital and 2 were found in subjects of 10 and 14 years I have examined a benign cystic teratoma removed surgically from the anterior mediastinum of a man aged 67 whose only symptom had been aching pain in the chest for 4 months

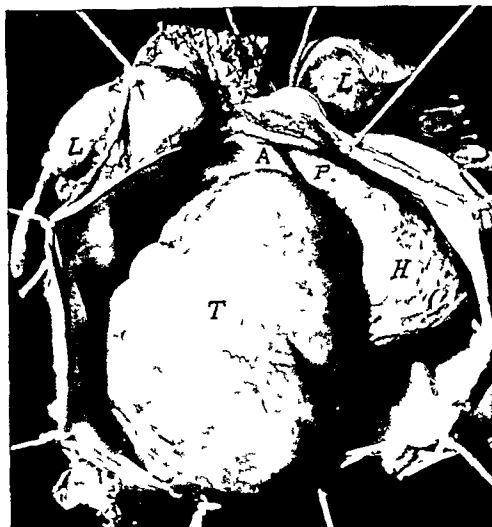


FIG. 468—Intra pericardial teratoma from a male infant as seen after reflexion of parietal pericardium T = teratoma H = heart A = aorta P pulmonary artery L lungs (Willis 1946) (Slightly reduced)

(d) Sex

The sexes are nearly equally affected with perhaps a slight preponderance of females, Hedblom's review included 79 males and 92 females Yet in striking contrast the malignant growths are almost restricted to males only 1 of the 25 cases reviewed by Houghton was a female

(e) Secondary results

The main complications include mechanical effects on the trachea great vessels heart or lungs infection and malignant change Infection may be followed

(1) Component tissues

It is unnecessary here to describe the commoner tissues in detail, it must suffice to enumerate them briefly. They are *adult* or *embryonic*, mature or immature. In benign cystic teratomas the tissues are of mature adult type and are easy to recognize, but malignant growths contain embryonic tissues of all degrees of immaturity the recognition of which often demands much experience. This is especially the case when these and well differentiated tissues are intermingled. Only those who are well acquainted with the histology of the embryo at different ages can hope to identify many of the components of the more malignant teratomas. It must be emphasized here that the tissues of malignant teratomas are

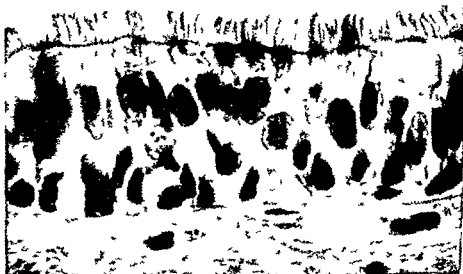


FIG 469—Ciliated respiratory epithelium in a teratoma (Iron haematoxylin stain) ($\times 1000$)

not merely anaplastic but truly embryonic, reproducing in structure and differentiation the tissues of the embryo and foetus. The mixture of differentiating tissues of all ages is one of the most striking structural characters of the malignant teratomas.

Skin, including hairs, sebaceous and sweat glands and rarely pigmented (Fischl) or exhibiting pigmented moles (Lubarsch), is a very common component. So are *stratified epithelium of oropharyngeal type* associated with lymphoid tissue and *mucous and mixed glands and respiratory pseudo stratified ciliated epithelium* (Fig 469). *Teeth* or masses of tooth formative tissue are frequent, usually solitary or few but sometimes numbering dozens or even hundreds. *Intestinal epithelium and glands* are often present. *Gastric and pancreatic tissues* are less frequent (Figs 470-471). *Liver tissue* has only occasionally been recorded (Corsy, Nicholson 1929 Fig 12). *Lung tissue* is very rare (Fig 472). *Nondescript glands* of various kinds are found—most of these are probably related to alimentary or respiratory structures. The identification of adipose skin covered eminences as *'mammary glands'* by Bland Sutton was fanciful.

members of the group have not been described, but the bearers of these growths seldom survive beyond the neo natal period

(b) Site

The epignathi are attached to the roof of the pharynx or palate from which they project into the mouth or nasal cavities. The base of the skull is not always affected, but in some cases the tumours have been hour glass shaped with intra cranial and extra cranial parts connected by an isthmus traversing the sphenoid as in the cases of Arnold and Kraus. It is clear that basal cranial and intracranial teratomas and epignathi differ only in the directions in which they tend to protrude as they grow. They all arise in the vicinity of Rathke's pouch, the oral membrane and the anterior end of the notochord.

(c) Age

With rare exceptions the tumours have been fatal in the foetus or new born infant. Their time of origin is clearly during early embryogenesis.

(7) Intracranial and intrathecal teratomas

Intracranial teratomas other than those arising from the base of the skull have been described and reviewed by Saxer, Askanazy, Barron, Hosoi, Harding and Naish, McLean, Bochner and Scarff, Dénes and Russell. I have studied the following two examples.

Case II—Male aged 10. *History*—Headache, vomiting and drowsiness for 7 weeks, child previously normal and intelligent. Examination showed papilloedema and ventriculograms showed great dilatation of third and lateral ventricles. *Necropsy*—Spongy vascular growth 3.5 centimetres in main extent replaced pineal gland, quadrigeminal plate, adjacent part of left pulvinar and filled and distended posterior half of third ventricle, aqueduct and upper half of fourth ventricle. Tumour extended into left choroidal fissure and projected slightly into lateral ventricle and there was a separate small area of growth on ventricular lining 1 centimetre from the main mass. Cerebellum compressed but not invaded. *Microscopical examination* showed a disorderly mixture of the following tissues: all immature and embryonic—squamous stratified epithelium, glands and irregular spaces lined by columnar epithelium, a few foci of neuro-epithelium, much undifferentiated epithelial tissue partly in the form of irregular networks and partly as diffuse or indefinitely clumped masses interspersed by collections of lymphocytes and therefore resembling seminoma in structure, much undifferentiated mesenchyme and occasional islands of young cartilage.

Case III—(Briefly recorded in 1944 by Dr R. Webster of Melbourne, who gave me one half of the specimen.) *Necropsy* on a female infant 9 weeks old with congenital hydrocephalus revealed a partly solid partly cystic teratoma 14 centimetres in main diameter which appeared to have arisen from the region of the basal ganglia and midbrain and which occupied the third and lateral ventricles and distended the cerebral cortex to a thin shell around it. The pineal corpus callosum and anterior commissure could not be identified; the pons and cerebellum were intact. *Microscopical examination* revealed a great variety of young tissues including much central nervous tissue, choroid plexus, pigmented neuro-epithelium, respiratory squamous stratified and columnar celled epithelia, various glandular structures, renal tissue, skin, immature teeth, bone, cartilage, adipose tissue, smooth and striated muscle fibres. These were partly well differentiated and partly embryonic and of different degrees of immaturity. Immature tissues predominated and much undifferentiated cellular epithelium and mesenchyme were also present.

cerebrospinal fluid, and (c) in malignant growths, *embryonic neuro epithelial tissue* forming tubules layers lining cavities, or irregular networks (Fig 473) and often

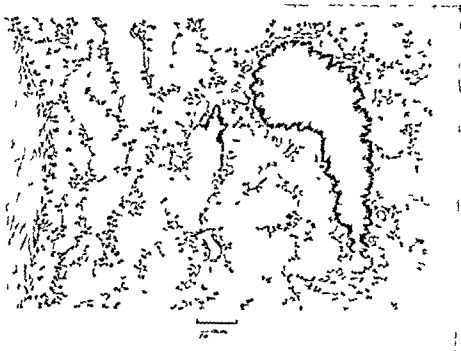


FIG 472 —Lung tissue in a teratoma of the brain from a female infant (*Drawing by G H Nicholson from specimen reported by Harding and Naish 1935*) ($\times 80$)

mistaken for glandular structures. Peripheral nervous tissue occurs as *nerve ganglia* of sympathetic type (see Fig 493), *nerve bundles* usually accompanied by plentiful Schwann cells, and usually non medullated but sometimes medullated,



FIG 473 —Embryonic neuro-epithelial plaques and tubules (N) in continuity with a simple epithelium (A) and with squamous stratified epithelium (E) in walls of small cavities (C) in a testicular teratoma (*Vo I Willis 1935 and 1936*) ($\times 45$)

and occasional well differentiated *Pacman corpuscles* (Kaboth, Hausmann and Berne Nicholson 1937 Fig 161, Willis, 1936, Masten) *Ocular tissue* is

Nervous tissue is present in at least four fifths of all teratomas (Willis, 1936)¹ Central nervous tissue occurs in benign growths as (a) masses of *neuroglial tissue* with characteristic staining properties usually astrocytic but sometimes containing



FIG 470 —Gastric mucosa from teratoma shown in Fig 468 ($\times 120$)



FIG 471 —Pancreatic tissue with islets of Langerhans from teratoma shown in Fig 468 ($\times 170$)

also oligodendrocytes (Willis Fig 6 Barnard Fig 7) usually devoid of but sometimes containing *nerve cells* and with or without *ependyma lined cavities* (b) small or large cavities lined by fringes of *choroid plexus* and containing

mass of immature renal tissue resembling that of a nephroblastoma (Fig 475) The cerebral teratoma of Case III above also contained embryonic renal tissue

Genital tissues have rarely been found Kaboth recorded the presence of uterine tissue with endometrium in an ovarian teratoma, I depicted (Fig 35, 1935) endometrium like tissue in a mediastinal teratoma and Truc and Guibert saw what they believed to be endometrial tissue with menstrual changes in a teratoma of the testis In none of these cases can the identity of the tissue be regarded as certain and Truc and Guibert's identification is particularly dubious The umbilical cords and 'placentas' which have been identified in teratomas are all imaginary Chorionic and "chorion epitheliomatous"

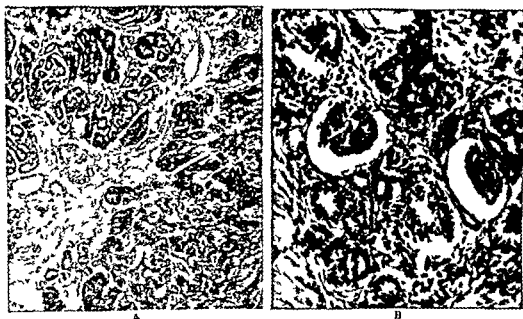


FIG 475—Embryonic renal tissue in a solid retroperitoneal teratoma from a female infant. A shows imperfect tubules and glomeruli and closely resembles nephroblastoma B shows nearly fully formed glomeruli (Willis 1935 Case X) ($\times 50$ and 100)

tissue is almost certainly only a form of anaplastic epithelial growth associated with haemorrhage (see Chapter 33) The ovarian tissue seen by Gordon in a small mediastinal tumour may have been altered thyroid tissue Testicular tissue has not been described except by Peyron who claimed to discover two nearly normal testes in a sacral teratoma from an infant 2 weeks old Peyron's description and diagrammatic drawings are however very unconvincing, and his many groundless identifications of primitive amniotic vesicles primitive streak, allantois gonoblasts polyembryos and blastocysts in malignant testicular teratomas discredit the reliability of all his observations in this field

Cartilage and bone in all stages of formation are very common So also are *adipose tissue connective and vascular tissue*, and in malignant growths undifferentiated *embryonic mesenchyme* *Haemopoietic tissue* is represented by bone marrow in masses of bone and by lymphoid tissue associated with oropharyngeal respiratory or intestinal epithelia

sometimes represented by cavities lined by folded layers of deeply pigmented epithelium resembling that of the ciliary body or by pigmented embryonic neuro-epithelium resembling that of the developing optic cup (Katsurada Abadie Corsy *et al*, Heijl, Kraus Dènes, and Fig 474), but no developed retina proper has been described and there is no justification for speaking of 'eyes' in teratomas

Thyroid tissue is not unusual, and it may be the bulkiest part of the growth Nicholson (1937) reviewed the subject of 'ovarian goitres' and rightly warned against assuming these all to be teratomatous without proof yet of 67 cases, teratomatous tissues were demonstrated in the same ovary in no fewer than 23 Neumann (1937) saw 8 examples of thyroid tissue in the ovary in 5 of these the tumours were obvious teratomas, in 2 others teratomatous tissues were found

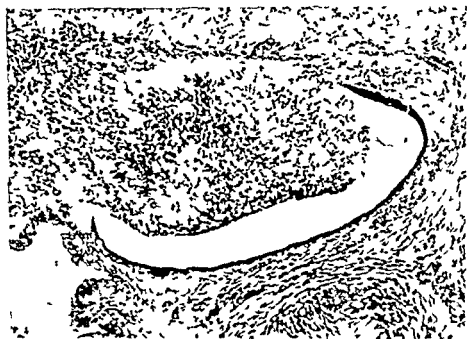


FIG 474 —Case III Small cavity in cerebral teratoma lined partly by embryonic nervous tissue and partly by deeply pigmented ocular epithelium ($\times 120$)

only after painstaking search of serial sections and of the remaining specimen, in which only thyroid tissue was found only part of the tumour was available for examination It seems safe to conclude that most specimens of ovarian thyroid tissue are certainly teratomatous and that this is probably true of all In Emge's first case thyrotoxic symptoms abated after removal of a thyroid containing ovarian teratoma in his second case one of seemingly pure ovarian goitre thyrotoxic symptoms developed along with recurrent peritoneal metastases of thyroid tissue and abated after removal of the metastasis laden omentum Emge reviewed 9 reported cases of ovarian goitre with metastases Thyroid tissue has only occasionally been seen in teratomas other than ovarian e.g. in the pineal teratoma described by Bochner and Scarff

Renal tissue has only rarely been seen in teratomas (Budde Nicholson 1934 Willis 1935 Cases X and XIII) My Case X was remarkable in containing a

organogenesis. Such tissue correlations attain their greatest complexity in those teratomas which contain highly organized parts, now to be described.

(3) Highly organized parts in teratomas

The most highly organized structures seen in teratomas include digits and other parts of limbs, pieces of intestine, pieces of cerebellum or cerebrum, sympathetic nerve ganglia and nerves, as well as those familiar components skin and teeth.

Digits and Limbs 'Limbs' have often been reported in teratomas when only digit bearing projections have been present. Nicholson (1935 and 1937) and Gale and Willis (1944) described carefully examined specimens of digit bearing teratomas, and reviewed many previous reports. Nicholson's 1937 paper contains the most complete description yet published of a tumour of this kind, his specimen was a sacrococcygeal teratoma containing three unusually

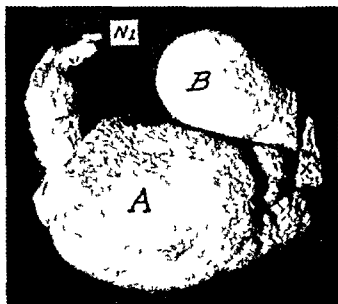


FIG. 477.—Intracystic mass bearing a digit from retroperitoneal teratoma in a girl aged 13. A and B = two bulbous parts of mass which were attached to cyst wall by pedicle X. N1 = nail at end of digit (Gale and Willis 1944) (Natural size)

well formed digits with nails, phalanges and metacarpals. The specimen which Gale and I examined was from a retroperitoneal teratoma and included a single digit bearing two nails and containing easily recognizable but imperfect phalanges and a metacarpal (Figs. 477-479). Other records of well developed digits, hands or 'feet' in teratomas include those of Böhm, Budde, Seegers, Brines and Love and Moersch. It is noteworthy that all of these concerned sacral or retroperitoneal tumours. None of the 'limbs' described in teratomas deserves this title, digits are the most that have been demonstrated and although bars or masses of bone proximal to these have been called 'pelvis', 'radius', etc., these identifications are fanciful.

Intestine sometimes occurs in the form of cavities lined by perfect intestinal mucosa and with a two layered muscular coat including an Auerbach's plexus or in the form of even more fully developed elongated coils projecting into a

Notochordal tissue has occasionally been reported, e.g. by Saver, Pandalar *et al* and by Riopelle. However, notochordal tissue is not very distinctive histologically and its identification in a teratoma must be very problematical. Pandalar *et al* properly recognized this difficulty by speaking of 'chordomatous' tissue. In Riopelle's case the nature of the vacuolated tissue is very uncertain because of the admitted alteration of the tissues by faulty fixation and decalcification.

Smooth muscular tissue is very common around alimentary or respiratory cavities. *Striated muscle* (Fig 476) is plentiful in some tumours and it is of interest that it may be abundant and well differentiated in a tumour in which peripheral nervous tissues are scanty or absent. This discrepancy raises the question whether teratomatous striated muscle can differentiate and maintain



FIG 476—Striated muscle fibres from same tumour as Fig 475 ($\times 375$)

its structure without any innervation. Studies of the innervation of muscle and other tissues in teratomas are needed. Katsurada's is I believe the only report of *cardiac muscle* in a teratoma.

(2) Tissue correlations in teratomas

At first glance the arrangement of the various tissues in teratomas, especially malignant ones, appears entirely haphazard and disorderly. Closer examination however soon discovers many characteristic associations of particular tissues resembling those of normal structures of the body (Nicholson Willis). Cavities lined by respiratory epithelium are often associated with cartilage; cavities lined by intestinal epithelium are often encircled by coats of smooth muscle; masses of central nervous tissue are often surrounded by meninges like sheaths and by masses of cartilage or bone. Teeth of course imply the orderly co-relation of epithelial enamel and mesenchymal dentine and they are moreover often set in well-developed bony sockets. These and other tissue relationships show the operation in the development of teratomatous tissues of dependent differentiation or the inductive effects of one growing tissue on another similar to those of normal

leptomeninges (Askanazy, Nicholson, 1929, Figs 8 and 9, Willis, 1935, Cases XI and XIII, and 1937, Cases XXIV and XXVIII) Well differentiated cerebellar cortex has been recorded by Askanazy, Landau, Willis (1939) and Bettinger

The degree of organization of *peripheral nerves and ganglia* in many teratomas is remarkable and raises interesting questions regarding the histogenesis and function of these structures. Thus nerves and nerve ganglia are often accompanied by abundant Schwann cells—what is the origin of these? Well developed nerve ganglia, usually of distinctly sympathetic type, are often found far removed from central nervous tissue or even in tumours in which such tissue is scanty or apparently absent, what is the origin of these ganglia? What tissues if any are innervated by the healthy looking nerves and ganglia which many teratomas contain and how are the developing nerves directed to their destinations? These questions must be answered by a closer study of the structure of teratomas of all ages and the answers will certainly be of interest to the student of the histogenesis of normal tissues. An interesting relationship was discovered by Nicholson in the digit containing teratoma described by him in 1937—the nerves which innervated the skin of the teratoma came from the sacral nerves of the patient. The organism treats the tumour as flesh of its flesh by supplying it with sensory nerves and the skin of the tumour reacts as a physiological part by supplying the appropriate receptors. An interesting research would be to examine a series of nerve containing teratomas by careful dissection or reconstruction, with the object of distinguishing nerves supplied by the host from intrinsic teratomatous nerves.

In considering highly organized structures in teratomas, it is well to recall that those very common components, *skin* and *teeth* are such structures. Teratomatous skin is often as perfect as normal skin, including well developed sebaceous and sweat glands hair follicles and arrector muscles. Teeth also erupted or unerupted with their enamel dentine pulp and paradental epithelial residues are far from simple structures—their formation involves interactions of the epithelial and mesenchymal tissues no less complex than those involved in the formation of a bone containing nail bearing digit. If teratomatous teeth were as rare as teratomatous digits they would excite the same wonder and lead to the same fanciful identifications of far more than is really present. Indeed even to day there are pathologists who would agree with Williams (1934) that teeth in a teratoma are evidence not only of an embryogenetic parasitic formation but also of cephalic derivatives thereof—heterotopic teeth being *residua* of the dental arcades of the parasite. Those who have read Nicholson's papers however and those who have examined a few teratomas properly, will on the contrary conclude that teeth do not presuppose a mouth or a digestive system nor digits a limb or trunk. Every highly organised part seen in a teratoma teaches the same lesson—namely that its appearance here does not depend on the presence of other parts to which in normal ontogeny, it is anatomically related. This last principle cannot be too strongly insisted on, those who will not admit it will continue to 'identify' all manner of things which are not present. (Gale and Willis)

coelomic cavity and possessing a peritoneal surface and a mesentery (Bohm, Hosmer, Kaboth, Hausmann and Berne, Schottenfeld and Littauer Willis, 1935 Case X Nicholson 1935, Fig 138)

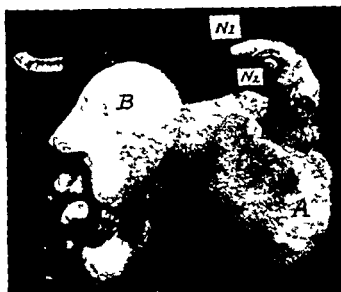


FIG 478 —Reverse aspect of mass in Fig 477 showing projecting bone and teeth near pedicle and a second sub-terminal nail (N2) a large detached part of which is shown in inset (Natural size)

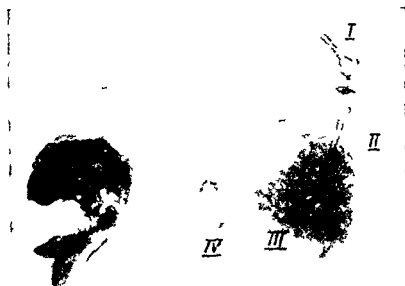


FIG 479 —Skiagram of mass shown in Figs 477 and 478 showing digital bones I and II other nondescript bones III and IV and mass of bone and teeth near pedicle (Natural size)

Highly organized central nervous structures are frequent. Masses of brain like tissue often contain central cavities lined by ependyma and choroid plexus and filled with clear cerebrospinal fluid and are often surrounded by delicate

in this plastic ectoderm like tissue accounts for the continuity of young nervous tissue and epidermis which is often to be seen in teratomas (Figs 480-484). In its later stages of differentiation teratomatous neural tissue resembles the spongioblastic mantle zone and the developing ependyma of the embryonic nervous system. As Nicholson observed, the development of choroid plexus in the walls

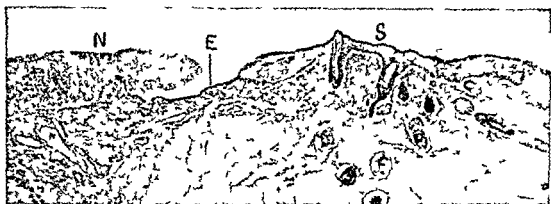


FIG. 482.—From same tumour as Figs 480 and 481, showing young nervous tissue (N) simple epithelium (E) and well formed young skin (S) in continuity with one another ($\times 45$)

of neuro epithelial cavities is related to the close contiguity of ingrowing vascular mesenchyme. Pigmented optic neuro epithelium is always associated with and clearly derived from ordinary non pigmented embryonic neural tissue. The histogenesis of peripheral nerves and ganglia, commented on above needs investigation.

The histogenesis of teratomatous teeth is closely similar to that of normal teeth. Tooth germs are developed in down growths of dental shelf tissue from cavities lined by ectodermal epithelium. mesenchymal dental papillae develop in relation

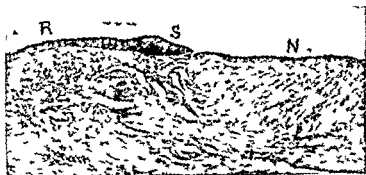


FIG. 483.—Continuity of respiratory epithelium (R) squamous stratified epithelium (S) and well differentiated neuroglial tissue (N) in an ovarian teratoma (Willis 1936 No 111) ($\times 55$)

to characteristic enamel organs with plentiful stellate reticulum, a bony alveolus often develops around the unerupted tooth, and paradental residues of the dental lamina are to be found in the periodontal tissues within the alveolus (Fig 465, and see Willis 1935 Fig 27). Subsequent eruption of teeth into the epithelial cavities from which they originated ensues. all the teeth in old benign teratomas have erupted. Defects in the enamel and dentine of old erupted teeth have been likened to caries, but the analogy is doubtful. the defects are probably disintegrative changes comparable with the desquamation of epithelium and its

(4) The histogenesis of teratomatous tissues

Teratomas especially those containing a mixture of embryonic and maturing tissues, afford many opportunities for studying the genesis and differentiation of tissues in abnormal environments. Small fragments of particular tissues are found growing in comparative isolation unassociated with structures to which they are

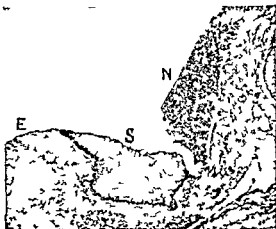


FIG 480 —From a malignant teratoma of the ovary showing a cavity lined by simple epithelium (E) squamous stratified epithelium (S) and young nervous tissue (N) continuous with one another (Willis 1936 No XV) ($\times 45$)

related in normal ontogeny. The malignant embryonic teratoma is a great conglomeration of multiplying plastic constituents the differentiation of which though seemingly haphazard must be determined by local chemical conditions and tissue relationships as in normal embryogenesis. What the teratomatous tissues can become in their scattered unanatomical positions is therefore of the greatest interest to students of normal histogeny. The teratoma also has this



FIG 481 —From same tumour as Fig 480 showing a cavity lined by squamous stratified epithelium (SS) young nervous tissue (N) and choroid plexus (P) ($\times 65$)

advantage over the normal embryo for such studies that it often contains a great variety of tissues at all stages of maturity and in all possible situations with respect to one another.

The histogenesis of teratomatous neural tissues was specially studied by the writer in 1936. It was shown that neuro epithelium takes origin from a simple plastic epithelium which like primitive embryonic ectoderm has also the potency of becoming epidermal or dental epithelium (Fig 473). Divergent differentiation

showed stages in the differentiation of nodules of hyaline cartilage from mesenchyme especially in the neighbourhood of masses of developing central nervous tissue, the differentiation of zones of non striated muscle around developing epithelial cavities (Fig 485), and the differentiation of striated muscle fibres in areas of undifferentiated spindle cells (Fig 486). Lymphoid tissue develops chiefly in the walls of oropharyngeal respiratory or intestinal cavities. I have never seen either a well circumscribed lymph gland or splenic tissue in a teratoma. Haemopoietic bone marrow is found only within masses of bone.

(5) Variations of structure possibly related to situation

I have been struck by the abundance of central nervous tissue in intracranial teratomas, by the frequent presence of plentiful gastric and pancreatic tissue in thoracic and upper abdominal teratomas, and by the fact that many of the teratomas containing digits or 'limbs' have been sacrococcygeal or retroperitoneal.



FIG 486—Thin striated muscle fibres revealed by iron haematoxylin stain in spindle celled tissue in a testicular teratoma (Willis 1935 Case I) ($\times 500$)

in position. Until a careful census is taken of all the tissues in a large series of teratomas, it would be unsafe to generalize on this subject, but I think it probable that the nature and quantities of the tissues in teratomas may be in part related to the level of the body where the growths take origin. This proposition merits study.

MALIGNANCY AND METASTASIS OF TERATOMAS

Malignancy in teratomas is of three distinct kinds. (1) In a benign cystic teratoma a malignant tumour may arise from one of the previously quiescent tissues of the growth. (2) In embryonic teratomas, like most of those of the testis, malignancy is a property of the whole growth, shared by all its immature tissues, though not necessarily in equal degrees, and (3) rarely relatively benign ovarian teratomas produce implants of one or more tissues in the peritoneum.

(1) Malignancy of a formerly benign cystic teratoma

This is most often squamous cell carcinoma arising from the skin of the growth, as in cases reviewed and described by Stewart and Eglinton. Masson

replacement by phagocytic granulation tissue which is so frequent in senile teratomas

The histogenesis of other epithelial tissues needs little comment. Skin, oro-pharyngeal and respiratory epithelia are often associated and in continuity with



FIG 484—Continuity of neuroglial tissue and glandular epithelium in the teratoma shown in Fig 466 ($\times 30$)

one another in the walls of cavities, and they can clearly arise from a common precursor. Salivary and other mixed glands develop as outgrowths from cavities lined by these epithelia. Pancreatic tissue is always associated with intestinal cavities, and ducts may be seen entering these cavities (Willis 1935 Fig 19)

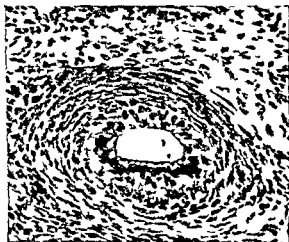


FIG 485—Early differentiation of smooth muscle in mesenchyme around a young glandular structure in a teratoma of the testis (Willis 1935 Case III) ($\times 225$)

Teratomas containing pancreatic tissue often contain gastric tissue also as in my intra pericardial specimen (Figs 470 471)

The histogenesis of mesenchymal tissues Embryonic teratomas often contain abundant undifferentiated mesenchyme and all stages can be traced in the development of muscle cartilage bone and connective tissue from this. My 1935 paper

was at least 14 and prior to confluence of neighbouring tumours, had probably been 22. All of the reported tumours have been of benign type, composed of fully differentiated tissues including skin, teeth, respiratory and alimentary epithelia, central nervous tissue, nerves and ganglia (Fig 493), cartilage, bone and adipose tissue.

In their benignancy the testicular teratomas of horses appear to contrast sharply with those of man, in whom malignant growths are the rule and benign ones the exception. It must be recalled, however, that the benign equine teratomas are found in colts corresponding in age to human children, and that most of the human testicular teratomas found during childhood are, like their equine counterparts, of benign type. Perhaps, then the seeming contrast between horse and man is largely accidental. Probably all human teratomas of the testis are present from early life in a benign form, and would be discovered unexpectedly at this stage if children were castrated as frequently as colts. Most human teratomas



FIG 493 —Well formed sympathetic ganglion cells and nerve fibres in specimen shown in Fig 492 ($\times 72$)

undergo malignant change in young adult life and become clinically evident only then. Perhaps some of the malignant testicular tumours seen in adult horses—which have often not been adequately studied or described—may be malignant teratomas similar to the human ones. More careful examination of the testes of gelded horses of various ages and of all equine testicular tumours along with more careful necropsy examination of young and old human testes may be expected to show the parallelism in the life histories of human and equine teratomas and to clear away some of the uncertainties regarding the genesis of these tumours.

(2) Gonadal teratomas in birds

Interest was focussed on avian teratomas by the Michalowsky (1926), later confirmed by Bagge (1936-7) that injection of a solution (also copper sulphate) into the testis of a bird led to the development of a teratoma.

discovery of
1) and by
Fahnestock
the rapid
respiratory

and Ochsenhurt, and Willis (1937) Rarely, carcinoma arises in some other epithelium, as in the cases of argentaffin carcinoma of ovarian teratomas described by Stewart, Willis and De Saram, and by Gabrilove and the cases of papillary



FIG 487—Case IV Squamous cell carcinoma of skin of ovarian teratoma ($\times 80$)

adenocarcinoma of sacrococcygeal teratomas described by Fletcher and Waring, Pringle, Pandalai *et al* Stewart *et al* and Lisco The 5 specimens showing supervening malignancy which I have studied all ovarian were briefly as follows

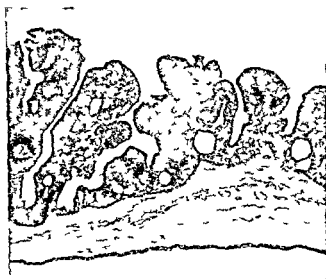


FIG 488—Case IV Pre invasive papillary carcinoma of teratomatous skin ($\times 30$)

Case IV—(No XVI 1937) Woman aged 67 operative removal of ovarian cyst 20 centimetres in diameter containing hairs and sebum Most of cyst wall was thin but in one place there was an eminence containing bone and 2 teeth and in another a projecting nodular mass of white growth 3 centimetres thick Microscopically this was squamous-cell carcinoma (Fig 487) Other parts of the cyst epithelium showed thickening papillary overgrowth and many mitoses (Fig 488) and was clearly cancerous but in the

(a) voices the formerly most popular, and still quite prevalent, view as to the nature of teratomas, often expressed in the term 'embryoma', (b) epitomizes the findings of the pathologist who has done more than any other to depreciate fantasy in the description of teratomas and to plead for 'uncoloured descriptions of specimens' and (c) is the conclusion of an experimental biologist who has realized that the careful objective study of teratomas holds much of interest for embryologists, and who incidentally, speaks of view (a) as 'this basic misconception

It would be of little value to repeat in detail here the many and various hypotheses which have been advanced regarding the nature of teratomas—that they represented included twins (*foetus in foetu*) that they arose from fertilized polar bodies, or from dislocated blastomeres that they resulted from ovarian pregnancies, or from parthenogenic (or ephebogenic) proliferation of the germ cells of the bearer or even that testicular teratomas arose from isolated ovarian cells fertilized in the testis (Langerhans, cited by Cawadiaz). Those interested in these earlier speculations will find them outlined and criticized in Askanazy's excellent review and in Nicholson's writings. It will however be of interest to mention doubts which were voiced even during the last century

(1) Early doubts regarding popular hypotheses

Peaslee's book on ovarian tumours (1873) contained a pertinent discussion of the 'ovarian pregnancy' and *foetus in foetu* hypotheses both of which he rejected. From the diversity and maturity of their tissues, he concluded that 'all dermoid cysts are congenital' and that 'their origin must be referred to a very early period of embryonic life' but he wisely abstained from formulating any definite hypothesis as to the nature of this early disturbance, saying, 'we must wait for the embryologist to answer these questions

The following remarks of Doran (1884) also are worth citing. The more pertinent question of the cause of the formation of these tumours in the ovary is a very profound one. Arguments must be founded on *data*, and I cannot see that we are in any way sure of our *data* in this case. In science we must seek how processes begin we cannot always hope to find out why they begin. To talk of parthenogenesis or of foetal inclusion is in reality, not giving an explanation. To explain the growth of hair, bone, teeth and glands in the ovary of an unimpregnated subject by saying that it is due to parthenogenesis is unscientific. It is more profitable to continue the examination of the tissues included within dermoid cysts than to indulge in speculations as to the origin of tumours of this class.

(2) The non foetiformity of teratomas

The hypotheses of twin inclusion, parthenogenesis or ephebogenesis have this in common that they postulate that a teratoma is essentially a foetus—a vertebrate organism. Consequently those who adopted these hypotheses strove to see signs of foetiformity in every teratoma and the literature of the subject teems with spurious identifications of structures which they believed they saw. 'If our expectation of seeing a thing is lively enough we will assuredly see it' (Nicholson 1934). Careful objective study of the structure of teratomas however shows

and alimentary epithelia, nervous tissues, cartilage bone striated muscle, etc. The results showed a striking seasonal difference most of the positive results being obtained (in the Northern hemisphere) when the birds were treated during the first 3 months of the year, i.e. when spermatogenesis was most active. Bagg, however, found that by the administration of pituitary gonadotrophic hormones successful results might be obtained as late as August.

What significance are we to attach to this peculiar result? In the first place it is to be noted that spontaneously occurring abdominal teratomas are not unusual in fowls, Mashar (1932) collected records of 13 examples. But in view of the numbers of tumours recorded by the Russian workers and by Bagg (about 30 in all) and the restriction of these to the treated testes, the view that these were fortuitously discovered spontaneous growths is untenable. So also Kahlau's negative results in a small series of fowls is of little significance, though his finding that cysts lined by squamous or mucous epithelium may result from metaplastic changes in the gonadal tissues at the site of injection is a reminder that such structures alone do not constitute teratomas. However, the tumours described by Falin and co workers contained young neural tissue, choroid plexus striated muscle, and other components not to be explained by simple local metaplasia. It seems clear, then, that genuine teratomas have been produced in birds testes by the introduction of zinc or copper salts. What relevance has this result for mammalian pathology? Does it disprove the origin of mammalian teratomas during embryonic life? I think not. On other grounds already discussed the early embryonic origin of mammalian teratomas seems so undeniable that we must not attach too great a significance to results in creatures of an entirely different class. Let us recall that the experimental teratomas of fowls are not the only avian tumours the analogy of which with human tumours is doubtful: there are also the filterable tumours and leucoses of birds which as was pointed out in Chapter 4, may not be comparable with mammalian tumours but may be peculiarly avian diseases. However this may be the experimental production of testicular teratomas in birds is a remarkable discovery and much more investigation of these tumours and their histogenesis is called for. There is need also of further attempts to produce tumours of mammalian gonads by the introduction of zinc salts or other substances (*see Willis 1934*).

THE NATURE AND HISTOGENESIS OF TERATOMAS

- (a) "A teratoma is an irregular conglomerate mass containing tissues and fragments of viscera belonging to a suppressed foetus attached to an otherwise normal individual" (Bland Sutton 1922)
- (b) A foetus without human form a body without regions organs without system shapes and proportions impossible absence of some unnatural multiplication of others—in short a light because it does not shine (Nicholson 1934)
- (c) 'What lies behind all the strange phenomena which we see in the teratomata is the failure of the individuation field at some point early in development to control the action of evocating substances' (Needham 1942)

differentiate with a promiscuity and apparent haphazardness which precludes any possibility of their derivation from definitive germ layers, and to designate particular components as ectodermal, endodermal or mesodermal while perhaps convenient descriptively, has no developmental meaning in these tumours. Moreover, they often show anomalous absence of a particular tissue, such as skin or nervous tissue or anomalous multiplicity of particular structures, such as hundreds of teeth, hundreds of separate little patches of nervous tissue, hundreds of intestinal or respiratory cysts—characters not exhibited by the most degraded amorphous foetuses.

(3) Teratomas the result of disturbed embryonic chemistry

Askanazy (1907) was the first I believe to draw attention to the significance of Spemann's discoveries for the study of teratomas. From his careful review of the structure and behaviour of these growths Askanazy concluded that they must arise from abnormal tissue primordia in early embryonic life, the primordium might develop synchronously with the host to form a benign cystic teratoma, a *teratoma adustum* or *coetaneum*, or the primordium might remain quiescent for years and then proliferate as a malignant embryonic teratoma. What, he asked, is the nature of this primordium? Is it a complex of different kinds of cells from all three germ layers or a self-differentiating germ with potencies equivalent to those of an ovum? The second alternative must be the correct one for Spemann had shown that organ rudiments are determined very early in embryonic life, and just as an optic cup has been shown to induce the formation of a lens in any region so it may well be that in the self-differentiation of ovi-equivalent teratoma germs similar inductive effects play an important part. Askanazy had thus attained to surprisingly modern concepts.

Not until two decades later did pathologists again turn to experimental embryology for light on the genesis of teratomas. In 1926, Budde discussed Spemann's work on the primary organizer and interpreted teratomas as the result of disturbances of the primitive streak. He drew attention especially to the situations of teratomas in median or paramedian positions from the base of the skull to the coccyx—a distribution strongly supporting the concept of anomalies of the primitive streak and its derivatives.

Like Nicholson and Needham I am convinced that Askanazy and Budde were right in seeking the clue to the nature of teratomas in the study of organizers or morphogenetic chemical substances of early embryonic development. The development of organoid structures in teratomas implies the interplay or mutual influence of neighbouring tissues on one another during their differentiation—influences of the nature of the embryologist's second grade and third grade organizers (see Needham, 1942 p. 290 *et seq.*). But however perfect the local products of such influences may be, the teratoma lacks all signs of the operation of a primary or first grade organizer that presiding and dominant organizer which initiates axiation and orderly somatic development and determines that a mass of plastic living stuff shall become a vertebrate organism. As Nicholson said (1935) "what I miss in the established teratoma is the co-ordinating action of a whole upon its parts in more scientific language evidence for the action at any stage of development of a dominant organizer for a body." Needham's

clearly the non foetiformity of these tumours. While it is true that some of the most reduced acardiac or amorphous fetuses lack demonstrable axial skeletons or regional parts as in Brodsky's specimen careful dissection or radiographic study reveals that most of them possess vertebrae and other regional bones or organs as in specimens described by Dietrich, Stewart (1914) Grogler (specimen No. 5), and van Tongeren (1932). This does *not* apply to teratomas *not a single specimen of teratoma with an indubitable spine or with a plainly somatic distribution of parts has been described*. Nicholson's detailed and critical examination (1934 and 1935) of supposedly foetiform teratomas (including the often cited specimens of Key, Repin, Shattock, Askanazy Ingier Heijl, Kaboth and Meyer) led him to conclude "that we do not accept foetiformity in a single object. Any unbiased reader of Nicholson's stimulating and amusing review will endorse this conclusion.

A point worth stressing here is that *incomplete examination of a teratoma can give it a false resemblance to a foetus*. Thus in No. XIII of my 1935 paper a single plane section of the growth (Fig. 28) could feasibly have been construed as showing a 'back' brain, "spinal cord", a series of vertebrae, and an 'alimentary system'. But complete examination shattered the illusion and showed that the seemingly anatomical distribution of parts in the one plane was accidental.

Here we must deal with the supposed 'vertebral column' in an ovarian teratoma described in 1940 by Riopelle. This 'vertebral column' was a cylinder 15 millimetres long consisting in the 'mid line' entirely of cartilage but containing on either side 3 ossified centres unequal in size and not symmetrically situated. Laterally the 'vertebral bodies' gave off short bony projections which curved backwards as neural arches partly fused into a single mass and devoid of articulations. The 'vertebral canal' contained a mass of central nervous tissue which was flanked by a series of ganglia from which issued nerves passing through 'invertebral foramina' in the investing bone. Those familiar with the development of the spine will find it difficult to desery that structure in a continuous cartilaginous rod with irregular bony areas and projections even if these skeletal tissues partially enclose some nervous tissue and ganglia and even if some patches of vacuolated cells thought to be notochord are found in the right half of the rudimentary spine. Nor is our confidence in Riopelle's identification enhanced by seeing (in his Fig. 2) that the spinal cord and brain were separated by a septum of connective tissue by observing that the spinal ganglia were nearly as large as the vertebral bodies and by reading of the plane of symmetry in what was clearly an asymmetrical structure. Riopelle's 'vertebral column' is in fact no more than an elongated partly cartilaginous partly bony mass encasing some nervous tissue—a well known relationship particularly commented on and depicted in my papers in 1935 and 1937.

Not only do teratomas lack the essential part of a vertebrate organism—a spinal axis—but they possess no organs or true somatic regions. They contain masses of central nervous tissue but no brain respiratory or intestinal cysts or canals but no respiratory or digestive systems renal tissue but no kidneys muscular tissue but no muscles. Teeth occur without a mouth tonsillar tissue without a pharynx and digits without a limb. In teratomas tissues and organoid structures

and mediastinal tissues via the oral membrane. It is significant that most cervical teratomas affect the thyroid gland which is a derivative of an outgrowth from the oral entoderm close to the oral membrane.

(5) The primordial tissue of teratomas

Study of the structure of teratomas shows that active growth depends on the presence of immature tissues. The most benign and quiescent teratomas consist of fully mature tissues with no signs of proliferative activity. The most malignant ones contain abundant immature embryonic tissues, some of them partially differentiated, some completely undifferentiated and resembling the tissues of very early embryos. All sorts of mixtures of mature and embryonic tissues are encountered in teratomas, and study of these mixtures makes it clear, as Jackson and Brues pointed out, that while some of the multiplying tissues go on to maturity and become relatively quiescent, some of them continue to multiply as undifferentiated embryonic tissue. It is this undifferentiated pluripotent tissue which is the essential parenchyma of the tumour; its differentiated tissues merely serve to show the range of its pluripotency. Teratomas and the embryonic tumours of the nervous system, kidney, liver and other parts have this in common that they arise from and consist of embryonic tissue which continues to multiply at the embryonic level. They differ in that while the embryonic tumours of particular organs have the stamp of regional determination upon them (though they show some latitude of differentiation not evinced by the normal parts) the teratomas are devoid or nearly devoid of regional determination. A teratoma is an embryonic tumour of pluripotential regionally non-specific tissue; it is from such tissue that it must originally have arisen, and it is such tissue that, save for maturational changes, it continues to consist of and to produce. This concept of teratomas does not conflict with their frequently complete maturation to form benign quiescent lesions, for so also do embryonic neuroblastomas sometimes undergo complete maturation to form relatively quiescent benign gangliogliomas.

The undifferentiated epithelial component of testicular teratomas (Figs 275 and 276, Chapter 33) may actually be the primordial tissue of these growths or something not far removed from it. Its relationships show that it is a highly plastic tissue capable of divergent differentiation into neuro-epithelium, epidermis and glandular epithelia, and that it is also the tissue which, when associated with haemorrhage or necrosis, often assumes a chorion epithelioma-like structure. I am still uncertain as to its capacity to produce mesenchymal tissues, though I have seen appearances which suggest this. If such a capacity were certainly established, then this tissue would indeed have all the potencies essential to our hypothetical teratomatous primordium and to the undifferentiated tumour parenchyma descended from it.

(6) Conclusion

The age incidence, site incidence, structure, mode of growth and differentiation of teratomas, along with a knowledge of recent advances in experimental embryology, all support the concept of teratomas developed in the preceding paragraphs. This is that teratomas are tumours arising from foci of plastic pluripotential embryonic tissue which escaped from the influence of the primary organizer during

identical conclusion has already been quoted at the beginning of this section

Krakka (1936) attributed teratomas to aberrant activity of the primary organizer, which ' may cause the production of secondary embryonic axes in the primitive shield and lead to the formation of a teratoma at any site ' This view essentially the same as Budde's must be rejected for the action of a primary organizer is as has just been insisted, the very thing that teratomas so plainly lack These growths must arise from tissue foci which in early embryonic life suffered some kind of physiological isolation from the influence of the primary organizer, so that they failed to participate in the normal architecture of the body and underwent instead differentiation along divergent lines determined by purely local factors Experiments by Durken Vogt, Kusche and Holtfreter well summarized by Huxley and De Beer and by Needham have shown that isolated parts of the morula or blastula, removed from the influence of the primary organizer, undergo chaotic differentiation into a variety of tissues in accordance with their own " labile determinations " Teratomas show every sign of similar chaotic differentiation strongly suggesting that their embryonic primordia escaped early from all external influences and proceeded to differentiate in accordance with their own intrinsic labile determinations The nature and cause of this escape are as yet unknown but increasing knowledge of the chemistry of the embryo will shed light on it Along with this elucidation there may well come also an explanation of the neoplastic quality of teratomas, which no doubt is intimately linked with the very chemical disturbance responsible for their genesis The study of teratomas is thus of double interest, on the one hand to the embryologist because it concerns problems of early organogenesis and histogenesis on the other hand to the student of tumour causation because the very nature of neoplasia may first be revealed by closer study of these growths and of the disturbances of sterol chemistry which determine their formation

(4) The situations of teratomas

The situations of teratomas to the significance of which Budde drew special attention call for further comment With relatively few exceptions teratomas arise in tissues which developmentally occupy immediately pre axial median or nearly median positions this applies to the gonadal sacrococcygeal retro peritoneal and cranial teratomas As Budde rightly held this distribution strongly suggests the operation of disturbances emanating from the embryonic primitive streak and its invaginated derivatives the notochord and adjacent structures

The only main exceptions to the rule that teratomas arise from tissues closely related to these structures are the anterior mediastinal and cervical teratomas which are separated from the dorsal axis by the thoracic and cervical viscera But are they really exceptions to the general rule ? Consideration of the early development of the head and neck shows that they are not In the early embryo when the oral membrane is still imperforate there is no neck and the rudiments of the heart and other thoracic organs are in close juxtaposition to the oral region It is only later when the head extends and the neck forms that the thoracic contents recede from their original juxta-oral position Chemical disturbances emanating from the anterior end of the notochord or adjacent tissues during early embryogenesis might readily be transmitted to the prospective anterior cervical

- Falin L I and Anissimowa W M (1940) *Z Krebsforsch* 50 339
 Falin L I (1941) *Z micro anat Forsch* 49 193
 Fenster E (1933) *Frankfurt Z Path* 46 403
 Fischl F (1933) *Z Geburts Gynak* 104 486
 Fletcher H M and Waring H J (1900) *Trans Path Soc Lond*, 51 226
 Fuller C B and Jagger F F C (1927) *Brit J Radiol* 32 176
 Fuss E M (1930) *Arch klin Chir* 159 515
 Gabrilove J L (1941) *Arch Path* 31 508
 Gale C W and Willis R A (1944) *J Path Bact* 56 403
 Gardner W S (1938) *Surg Gyn Obst* 67 455
 Geinitz J (1862) *Disch Klinik* 14 216
 Gordon I (1930) *Frankfurt Z Path* 40 224
 Griffiths T D (1877) *Trans Path Soc Lond* 28 196
 Grogler F (1933) *Virchows Arch* 289 430
 Harding H E and Naish A E (1935) *Lancet* i 77
 Hausmann G H and Berne C J (1932) *Arch Surg* 25 1090
HEDBLOM C A (1933) Intrathoracic dermoid cysts and teratomata with a report of six personal cases and 185 cases collected from the literature *J Thorac Surg* 3 22 (A valuable review)
 Hehl C F (1929) *Virchows Arch* 271 670
 Helmke K (1938) *Virchows Arch* 302 509
 Herzog G (1917) *Beitr path Anat* 63 755
 Heusinger C F (1865) *Virchows Arch* 33 177
 Himwich H E (1921) *J Cancer Res* 6 261
 Hipsley P L (1942) *Med J Austral* ii 63
 van der Horst H and Aboukhalil E (1933) *Ann Anat path* 10 454
 Hosmer A (1880) *Boston Med Surg J* 102 61
 Hosoi K (1930) *Arch Path* 9 1207
 Houghton J D (1936) *Amer J Path* 12 349
 Huxley J S and De Beer G R (1934) *The Elements of Experimental Embryology* Cambridge
 Inger A (1908) *Beitr path Anat* 43 356
 Jackson E B and Brues A M (1941) *Cancer Res* 1 494
 Jacobs W F (1929) *Amer J Path* 5 275
 James K L (1938) *Brit Med J* i 1311
KABOTH G (1924) Über die Morphologie und Genese foetusartiger Ovarialteratome *Arch Gynak* 122 803 (One of the most fully described foetiform teratomas See Nicholson's critique 1935)
 Kahlau G (1937) *Frankfurt Z Path* 50 281
 Kanthack A A and Pigg T S (1898) *J Path Bact* 5 78 and 89
 Kantrowitz A R (1934) *Amer J Path* 10 531
 Katsurada F (1901) *Beitr path Anat* 30 179
 Koltonski H (1920) *Z Krebsforsch* 17 408
 Krafka J (1936) *Arch Path* 21 756
 Kraus E J (1929) *Virchows Arch* 271 546
 Landau M (1912) *Frankfurt Z Path* 11 120
 Lexer E (1900) *Arch klin Chir* 61 648
 Lisco H (1942) *Ann Surg* 115 378
 Love J G and Moersch F P (1938) *Arch Surg* 37 949
 Lubarsch O (1932) *Virchows Arch* 285 197
 Mashar U (1932) *Virchows Arch* 285 155
 Masson J C and Ochsenhurn N C (1929) *Surg Gyn Obst* 48 702
 Masten M G (1940) *Arch Path* 30 755
 Mayer K (1930) *Zbl Gynak* 54 2328
 McCrea E D A (1930) *Brit J Surg* 18 91
 McLean A J (1935) *Surg Gyn Obst* 61 523
 McFarland J (1933) *Amer J Path* 9 271
 Meyer R (1925) *Arch Gynak* 123 714
 Michalowsky I (1926) *Zbl allg Path* 38 585

early embryonic development, this escape being in some way related to disturbances emanating from the invaginated organizing tissues of the primitive streak and so affecting median or para median parts in close relationship to these tissues. The affected primordium as it grows differentiates in accordance with its own intrinsic 'labile determinations', producing a variety of tissues foreign to the part in which it grows. If these tissues differentiate and mature as fast as they grow a benign cystic teratoma results. If the tissues fail to mature completely but retain their capacity for continued growth at the embryonic level a malignant embryonic teratoma results. In some teratomas, notably in the testis this capacity may be retained for many years by a small dormant teratomatous focus, which later evinces active growth and appears clinically as a progressive tumour during young adult life. Such dormancy, though of great interest and meriting the closest study, is not peculiar to teratomas—other kinds of malignant tumours also may display prolonged dormancy in recurrence or metastasis.

REFERENCES

- Abadie J (1924) *C R So Biol* 92 98
 AHLFEID, F (1875) Beiträge zur Lehre von den Zwillingen. Der Epignathus. *Arch Gynäk* 7 210 (A full and excellent review of earlier records)
 Arnold J (1870) *Virchows Arch* 50 482
 Aschheim S (1932) *Z Geburts Gynäk* 103 652
 ASKANAZY, M (1907) Die Teratome nach ihrem Bau, ihrem Verlauf, ihrer Genese und im Vergleich zum experimentellen Teratoid. *Verh Dtsch path Ges* 11 39 (The best account of teratomas to that date, still worthy of close study)
 Bagg H J (1936) *Amer J Cancer* 26 69
 Bagg H J (1937) *Science (Suppl)* 85 92
 Barnard W G (1931) *J Path Bact* 34 389
 Barron M (1916) *J Cancer Res* 1 311
 Bettinger H F (1941) *J Path Bact* 53 284
 Bland Sutton J (1889) *Dermoids*. London
 Bland Sutton J (1922) *Tumours, Innocent and Malignant*. London
 Bochner S J and Scarff J E (1938) *Arch Surg* 36 303
 Böhm F (1872) *Berl klin Wschr* 9 56
 Bosse M D (1940) *Amer J Cancer* 39 343
 Brines R J (1934) *J Amer Med Assoc* 103 338
 Brodsky I (1939) *Med J Austral* 1 539
 Bucy P C and Buchanan D N (1935) *Surg Gyn Obst* 60 1137
 Budde M (1926) *Beitr path Anat* 75 357
 Carmichael R and Oldfield C (1934) *J Path Bact*, 39 617
 Cawaduas A P (1941) *Brit Med J* ii 818
 Ceelen W (1912) *Virchows Arch* 207 178
 Chapman F D (1941) *Arch Path* 32 217
 Corsy F (1924) *C R Soc Biol* 90 572
 Corsy F, Dome H and Plantevin P (1926) *C R Soc Biol* 94 93
 Craver L F and Stewart F W (1936) *J Amer Med Assoc* 106 1802
 Crosby E H and Graham A (1932) *J Amer Med Assoc* 98 1789
 Denes J (1940) *Amer J Cancer* 40 329
 Dietrich A (1905) *Verh Dtsch path Ges* 9 198
 DORAN A H G (1884) *Clinical and Pathological Observations on Tumours of the Ovary, Fallopian Tube and Broad Ligament*. Chapter V. London
 Emge L A (1940) *Amer J Obst Gyn* 40 738
 Falin L I (1940) *Amer J Cancer* 38 199
 Falin L I and Gromzowa K E (1940) *Virchows Arch* 306 300 and 578

- Stewart M J (1914) *Proc Roy Soc Med* 7 (Gyn Sec) 131
- Stewart M J and Eglinton C (1911) *J Obst Gyn* 20 230
- Stewart M J, Willis R A and De Saram G S W (1939) *J Path Bact* 49 207
- Symeonidis A (1934) *Beitr path Anat* 94 370
- Thomson J G (1945) *J Path Bact* 57 213
- Thornton J K (1874) *Trans Path Soc Lond* 25 190
- Thornton J K (1876) *Ibid* 27 209
- van Tongeren F C (1932) *Zbl Gynak* 56 594
- Truc E and Guibert H L (1939) *Bull Assoc franç Cancer* 28 480
- Virchow R (1871) *Virchows Arch* 53 444
- Wakeley C P G (1933) *Surg Gyn Obst* 56 692
- Wakeley C P G (1938) *Brit J Surg* 26 443
- Webster R (1938) *Med J Austral* ii 104
- Webster R (1944) *Ibid* ii 196
- White W H (1885) *Trans Path Soc Lond* 36 37
- Williams W R (1934) *J Obst Gyn* 41 721
- Williams W R (1935) *Teratoid Tumours With Special Reference to the Sacro coccygeal Group*
London
- Willis R A (1934) *Brit J Exp Path* 15 234
- WILLIS, R A (1935 and 1937) The structure of teratomata *J Path Bact* 1935 40 1
1937 45 49 (A detailed description of 18 specimens)
- WILLIS, R A (1936) The neural components of teratomata *Med J Austral* i 231
- WILLIS R A (1936) The histogenesis of neural tissue in teratomas *J Path Bact* 42 411
- Willis R A (1938) *Ibid* 46 198
- Willis R A (1939) *Ibid* 49 571
- Willis R A (1946) *Ibid* 58 284
- WILLIS R A and RUDDUCK H B (1943) Testicular teratomas in horses *Ibid*
55 165
- WILMS, M (1896) Die teratoiden Geschwulste des Hodens mit Einschluss der sog Cystoide
und Enchondrome *Beitr path Anat* 19 233 (A useful account of the older records)
- Zerman P (1943) *Med J Austral* ii 315

- Montgomery A H (1922) *J Amer Med Assoc* 78 416
- Morgen M (1924) *Virchows Arch* 249 217
- Muller A (1905) *Arch klin Chir* 76 661
- NEEDHAM J (1936) New advances in the chemistry and biology of organized growth ,
Proc Roy Soc Med 29 1577
- NEEDHAM, J (1942) *Biochemistry and Morphogenesis* pp 231 *et seq* 290 *et seq* Cambridge
(A biologist's views on teratomas which every pathologist should read and ponder)
- Neumann H O (1937) *Arch Gynak* 163 600
- Nicholson G W (1907) *Guy's Hosp Rep* 61 249
- NICHOLSON, G W (1929) The histogeny of teratomata *J Path Bact* 32 365
- NICHOLSON G W (1930) The teratomata *Guy's Hosp Rep* 80 384
- NICHOLSON G W (1934) Kidney in a teratoma *ibid* 84 140
- NICHOLSON G W (1934) A foetiform ovarian teratoma (A redescription of Mr S G Shattock's case) *ibid* 84 389
- NICHOLSON G W (1935) Foetiform ovarian teratomata *ibid* 85 8
- NICHOLSON G W (1935) A foetiform teratoma *ibid* 85 379
- NICHOLSON G W (1937) Sacral teratoma with digits *ibid* 87 46
- NICHOLSON G W (1937) Ovarian goitre *ibid* 87 391
- Novak E (1941) *Gynecological and Obstetrical Pathology* Philadelphia
- OHKUBO, S (1908) Zur Kenntnis der Embryome des Hodens *Arch Entwicklungsmechanik*
26 509 (The best of the earlier reviews of testicular teratomas)
- Ottow B (1930) *Z Geburts Gynak* 97 487
- Paget J (1855) *Medico Chir Trans* 38 247
- Pandalai K G Forsyth W L and Stewart M J (1924) *J Path Bact* 27 139
- Parker R W (1885) *Trans Path Soc Lond* 36 299
- Peaslee E R (1873) *Ovarian Tumours* London
- Penberthy G C and Brownson K M (1938) *Ann Surg* 107 566
- Peyron A (1939) *C R Soc Biol* 130 1470 and 1577
- Peyron A (1939) *Bull Assoc franç Cancer* 28 658
- Peyron A and Limousin H (1936) *C R Soc Biol* 123 409
- Port H (1880) *Trans Path Soc Lond* 31 307
- Potter E L (1938) *Arch Path* 25 639
- Pringle S (1907) *Lancet* 1 1643
- Prym P (1925) *Dtsch med Wschr* 51 1149
- Prym P (1927) *Virchows Arch* 265 239
- Pusch L C and Nelson C M (1935) *Amer J Cancer* 23 791
- Randall M and Lawrence T W P (1927) *Proc Roy Soc Med* 21 (Gyn Sec) 105
- Riopelle J L (1940) *Amer J Path* 16 625
- Ritchie J (1903) *J Obst Gyn* 4 65
- Rosenbach F (1906) *Arch klin Chir* 81 635
- Ross J M (1932) *J Path Bact* 35 563
- Roth W (1916) *Beitr path Anat* 61 42
- Russell D S (1944) *J Path Bact* 56 145
- Saphir O (1929) *Amer J Path* 5 313
- Saxer F (1896) *Beitr path Anat* 20 332
- Schauberger W (1938) *Zbl allg Path* 70 161
- Schmeel W (1909) *Frankfurt Z Path* 2 232
- Schonholzer G (1907) *Beitr path Anat* 40 349
- Schottenfeld L E and Littauer E V (1938) *Amer J Obst Gyn* 35 889
- Seegers W (1934) *Beitr path Anat* 93 491
- Shapiro P F (1930) *Ann Surg* 92 1031
- Shattock C E (1923) *Brit J Surg* 10 334
- Sippel A (1924) *Zbl Gynak* 48 85
- Smadel J E (1936) *Amer J Cancer* 26 316
- Stammmler M (1934) *Verh Dtsch path Ges* 27 190
- Steinert H (1903) *Virchows Arch* 174 232
- Stewart J D Alter N M and Craig J D (1930) *Surg Gyn Obst* 50 85
- Stewart M J (1913) *J Path Bact*, 17 502

of disseminated growths in remote organs but without a demonstrable primary tumour in the uterus or tubes, have often been recorded (Zagorjanski Kissel, Munzer, Busse Dungen Walthard, Polano Christeller and Oppenheimer, Lapointe *et al* Brews Brown *et al*) The interpretation of such cases is often uncertain We must first exclude possibly spurious cases in which a haemorrhagic carcinoma or teratoma may have been mistaken for chorion epithelioma but a number of unquestionably genuine chorion epitheliomas will remain There are two alternative explanations of these—either the seemingly primary extra genital growth was really a metastasis of a uterine or tubal primary tumour which had



FIG. 494 —A mass of chorionic syncytium in a large vein in a tubal pregnancy ($\times 120$)

disappeared, or it was a genuine primary tumour arising from deported chorionic elements There is little doubt that both of these events do occur, but in many cases it is difficult to decide which of the alternative explanations is the correct one It is well known that in both normal pregnancy and in cases of hydatidiform mole emboli of chorionic epithelium or even entire placental villi are transported by the blood stream and lodged in neighbouring pelvic tissues and in the lungs (Pick Veit, Marchand Dungen, Stevens, Hughes) It is quite probable that extra genital primary chorion-epithelioma may occasionally take origin from these transported elements Relevant in this connexion also is the unusual condition of benign multiple implants of chorionic villi found by Lazarus and Schiffrin in various parts of the peritoneal cavity

(3) Hydatidiform mole

About 50 per cent of chorion epitheliomas are known to be preceded by hydatidiform moles 25 per cent by abortions, and 25 per cent by apparently normal pregnancies (Novak Brews) Since mild degrees of hydatidiform change often escape recognition (Hertig and Edmonds) it is probable that this

CHAPTER 62

CHORION EPITHELIOMA

CHORION EPITHELIOMA is unique in being a tumour of one individual transferred to another—a foetal tumour affecting the mother. Discussion of its histogenesis is unnecessary, there is now universal recognition of its origin from the chorionic epithelium, and of the erroneous nature of the old name *deciduoma malignum*. It is a rare tumour but it is impossible to assess its frequency accurately, because of the difficulty of distinguishing between invasive moles with atypical tissue and genuine chorion epitheliomas.

AGE INCIDENCE SITE AND CAUSATION

(1) Age incidence

As might be expected most chorionic tumours appear in women of child bearing age usually between 25 and 45 years. The interval elapsing between termination of the offending gestation and development of the tumour is usually only a few weeks or months, occasionally 2 or 3 years (as in Dunger's case) and rarely longer (e.g. apparently 8 years in the case reported by Brown *et al*). As Novak pointed out, in cases with these long latent periods, the possibility of there having been an unsuspected intervening conception can rarely be excluded. Post menopausal chorion epithelioma is very rare.

(2) Site

(a) *Primary uterine chorion epithelioma*

The uterus is the primary site of the disease in at least 90 per cent of cases. In the uterus the growth arises from retained placental tissue following either normal pregnancy and delivery or abortion, with or without hydatidiform mole. There is good evidence that a primary uterine growth may sometimes be so small as to be removed by simple curettage yet may have produced metastases (Novak and Koff), and such cases are difficult to distinguish from those in which the primary growth arises not from residual chorionic tissue in the uterus but from tissue already deported to other situations (see below).

(b) *Primary tubal or ovarian chorion epithelioma*

Many instances of chorion epithelioma of a tubal gestation have been reported (Risel 1905, Thomas, Williams and other references by Lazarus and Schürf). Supposed cases of primary ovarian chorion epithelioma are difficult to interpret. Risel (1914) described a case of disseminated chorion epithelioma of seemingly ovarian origin but the uterus showed a pigmented area which Risel regarded as evidence of a former uterine growth which had been expelled and this possibility remains also with other reported cases.

(c) *Primary chorion epithelioma in other sites*

Cases of chorion-epithelioma of the vagina, vulva or other pelvic organs, or

which this mistake has been made will, of course, show a high proportion of moles giving rise to "chorion epithelioma" Estimates vary between 1 per cent and 40



FIG 497 —Invasive hydatidiform mole a large villus accompanied by much chorionic epithelium within a vein in the myometrium ($\times 100$)



FIG 498 —Invasive hydatidiform mole a mass of chorionic epithelium in a large vein in the outer myometrium ($\times 120$)

change precedes chorion epithelioma in the great majority of cases. The proportion of cases of hydatidiform mole to become chorion epitheliomatous is difficult to



FIG 495 —Hydatidiform mole a large oedematous villus with masses of overgrown chorion epithelium ($\times 40$)

assess, partly because the milder degrees of the change escape diagnosis and partly because invasive moles have often been mistaken for chorion epitheliomas. Series in



FIG 496 —Detail of Fig 495 ($\times 120$)

hydatidiform mole, in animals Ratchliffe reported having seen a rodent, *Erithezon dorsatum*, and Schlotthauer a dog, with chorion epithelioma, but without giving adequate details

STRUCTURE OF CHORION EPITHELIOMA

The grossly haemorrhagic and necrotic characters of this tumour are well known Microscopically (Figs 499, 500) areas of well preserved tumour tissue consist of irregular masses of polyhedral cells and fused syncytial masses These are sometimes distinctive enough to be reminiscent of the hyperplastic chorionic epithelium of retained or hydatidiform placenta, but in many of the tumours the tissue is anaplastic and shows no real resemblance to its normal prototype Invasion of blood-vessels and mingled tumour and haemorrhage are prominent features

While the identity of a uterine tumour of this kind is clear enough, mistaken diagnoses of "chorion epithelioma" have often been made with other tumours merely because they have been haemorrhagic and have shown anaplastic growth



FIG 500 —Detail of Fig 499 ($\times 150$)

with syncytia It is to be insisted that the structure of chorion epithelioma is often not diagnostically distinctive and that it can be mimicked by anaplastic carcinoma, e.g. of the stomach or liver, and anaplastic teratoma of the testis or other parts (q v)

METASTASIS

The proclivity of chorion epithelioma to invade veins (see Schlagenhauser, Schmauch Teacher, Cary) explains the predominance of blood borne metastases in this disease Lymph nodal metastases also occur, but are relatively infrequent and of little clinical importance

per cent or more, I agree with Novak that the lower figures are nearer the truth

Normal chorionic tissue can often be found invading veins in the wall of the uterus or tube and invasive mole may extend widely in this way and may show great syncytial overgrowth yet may be clinically benign (Figs 494-498) Invasion of veins does not *per se* denote malignancy which can be diagnosed confidently only when destructive extravascular extension is present Microscopical distinction between atypical invasive mole and early chorion-epithelioma is difficult and not always possible It is probable that benign hydatidiform mole, invasive mole (chorio-adenoma destruens) and chorion-epithelioma form a continuous series with all transitions between them

The structure and genesis of hydatidiform mole were carefully studied by Hertig and Edmonds who concluded that in most cases this disease is probably the result of early failure or defective development of the embryo so that no foetal



FIG 499—Chorion-epithelioma invading a large vein in the wall of the uterus ($\times 80$)

circulation develops in the villi Brews also pointed out that since fertility after a hydatidiform mole is often normal the factors responsible for the latter lie in the ovum rather than in endocrine or other abnormalities of the mother The nature of these factors is however still unknown

(4) Chorion-epithelioma in animals

I have not encountered any clear reports of chorion-epithelioma or of

- HERTIG, A T, and EDMONDS, H W (1940) *Genesis of hydatidiform mole* *Arch Path*, 30 260 (An important and well illustrated study)
- Hughes J E (1930) *Proc Roy Soc Med* 23 1157
- Kelly J K and Teacher J H (1898) *J Path Bact*, 5 358
- Lapointe A, Caine A and Darfeuil L (1931) *Ann Anat path* 8 425
- Lazarus J A and Schiffrin A (1942) *Ann Surg* 115 93
- Lufu M and Schukru M B (1933) *Beitr path Anat* 90 666
- Marchand F (1903) *J Obst Gyn* 4 74
- Munzer M (1902) *Zbl allgem Path* 13 197
- Novak E (1941) *Gynecological and Obstetrical Pathology*, Chapter XXXIII Philadelphia
- Novak E and Koff A K (1930) *Amer J Obst Gyn* 20 153
- Pick L (1897) *Berlin klin Wschr* 34 1069 1097
- Polano O (1914) *Z Geburts Gynak* 75 149
- Ratcliffe H L (1933) *Amer J Cancer* 17 116
- Risel R (1914) *Verh Dtsch path Ges*, 17 386
- Risel W (1905) *Z Geburts Gynak* 56 154
- Rossler H (1929) *Z Geburts Gynak* 96 516
- Scheidemandel E (1908) *Berlin klin Wschr* 45 740
- Schlagenhauser F (1899) *Wien klin Wschr* p 486
- Schlotthauer C F (1939) *J Amer Vet Med Assoc* 95 181
- Schmauch G (1907) *Surg Gyn Obst* 5 259
- Steinhaus J (1899) *Zbl allgem Path* 10 55
- Stevens T G (1927) *Clin J* 56 133
- Teacher J H (1908) *J Path Bact* 12 487
- Thomas R C (1934) *Brit Med J* ii 590
- Veit J (1901) *Z Geburts Gynak* 44 466
- Walthard M (1907) *Z Geburts Gynak* 59 443
- Williams T J (1938) *Amer J Obst Gyn* 35 863
- Willis R A (1934) *The Spread of Tumours in the Human Body* London
- Zagorjanski Kassel (1902) *Arch Gynak* 67 326

(1) Regional venous embolic metastases

Blood borne metastases due to local retrograde embolism in the vulvo vaginal or other pelvic veins develop frequently. They appear as bluish or purple nodules in the vulva, vaginal walls, bladder or broad ligaments and they are sometimes the first indications of disease (Munzer Teacher, Schmauch, my Case 219 recorded in 1934, and Brews's Case 11). These local venous metastases doubtless result from occlusion of large metrial and parametrial veins and consequent retrograde diversions of venous flow with tumour emboli into tributary vessels. Metastases in the ovaries (Steinhaus, Risel 1914, Lufti and Schukru) are probably attributable to local venous embolism more often than to general dissemination.

(2) Remote metastases

These occur first in the lungs, often causing haemoptysis which is sometimes the first sign of the disease (Kelly and Teacher, Scheidemandel, Brown *et al*). Dissemination beyond the lungs often produces metastases in many other viscera especially spleen, intestines and brain. My 1934 review of 25 necropsy records in cases with blood borne metastases showed the lungs affected in 23 cases, spleen in 15, intestine 15, brain 14, kidney 14, liver 13, pancreas 3, thyroid 2, stomach 2, heart 1, adrenals 1 and bone 1. In 9 cases in which the spleen or intestines contained metastases, the liver nevertheless escaped. Lufti and Schukru's case had metastases in the pituitary, thyroid, adrenals, gastric and duodenal mucosa, as well as more usual sites.

HORMONAL RESULTS

Both hydatidiform mole and chorion epithelioma are frequently accompanied by multiple luteal cysts of the ovaries and these are clearly the result of hormonal disturbances produced by the mole or tumour for they regress on removal of the latter. The strongly positive Aschheim Zondek test in cases of hydatidiform mole and chorion epithelioma is due to the secretion by these of gonadotrophic hormone similar to that of the normal placenta. Rise or fall of the hormone titre in a case of mole or tumour under treatment is an important diagnostic and prognostic test (Rossler, Gerritzen, Cosgrove, Cuscaden and Bettinger). By follow up tests in a case of hydatidiform mole Cuscaden and Bettinger detected and successfully treated an early chorion epithelioma of the uterus. Extra uterine chorion epithelioma like extra uterine pregnancy produces decidual changes in the endometrium (Zagorjanski, Kissel, Busse, Marchand, Christeller and Oppenheimer).

REFERENCES

- Brews A (1935) *Proc Roy Soc Med* 28 1213
 Brown A F, Snodgrass W and Pratt O B (1940) *Amer J Cancer* 38 564
 Busse O (1903) *Virchows Arch* 174 207
 Cary E (1913) *Surg Gyn Obst* 16 362
 Christeller F and Oppenheimer P (1925) *Virchows Arch* 257 691
 Cosgrove S A (1938) *Amer J Obst Gyn* 35 581
 Cuscaden W G and Bettinger H F (1940) *Med J Austral* 4 377
 Dunger R (1905) *Beitr path Anat* 37 270
 Gerritzen F (1931) *Zbl Gynak* 55 545

INDEX

Breast (*cont*)

carcinoma of (*cont*)

- lymphatics permeated by 154-156 167 240-241
- marital state and 226
- menstrual history and 227
- metaplasia in 238-239 240 241
- metastasis of 138 167-168 171 178 209 242-245
- milk factor and 51 226
- mode of origin of 117 231-233 234-237
- mortality rates of 223-226
- mucoid 126 128 238-240
- multicentric origin of 117 209 231-233
- oedema of arm from 210
- operability of 209
- ovarian factor in causation of 48-51 230 246
- Paget's disease with 247-255
- peau d orange with 240
 - pig skin with 240
- prognosis of 242-243
- race incidence of 223-228
- recurrence of delayed 209 244
- reproductive history of 226-228
- satellite nodules with 240-241
- shape of 122
- sites of 234-235
- social incidence of 88 228
- spread of 154-156 239-245
- squamous 126 239 241
- statistics of 223-228
- structure of 128 234-241
- surgery of 123-4
- telangiectatic type of 160 241
- thyrotoxicosis associated with 233
- trend of 225-226
- tuberculosis associated with 234
- variation of structure in 128 235 238
- carcino sarcoma of 218
 - chronic mastitis of 229-233
- cystic disease of 229-233
- cystic hyperplasia of 117 124 229-233
- cystosarcoma phyllodes of 216
- epithelial tumours of 208-255
- fibro-adenoma of 211-220
 - age incidence of 212
 - bone and cartilage in 102 139 212-213 216 220
 - calcification in 216
 - carcinomatous change in 218
 - fat cells in 216 221
 - giant form of 208 216-220 221
 - in animals 50 94 95 97 101-102 130 139 211-213 220
 - in males 212
 - incidence of 210 212
 - lactation in 130 216
 - malignant change in 101 102 140 213 218-220
 - mode of origin of 118 214
 - mucinous change in 216
 - sarcoma of 101 102 140 213 218-220
 - shape of 122 214

INDEX

- Abdominal walls fibroma of 649 650-651
 - lipoma of 658
 - myxosarcoma of, 653
 - secondary tumours of 407
- Acanthoma 269 270
- Acanthotic naevus 268
- Acetylamino-fluor. mol. 46-47
- Acoustic nerve, tumour 720 828-829 832 838
- Acromegaly 63 639
- Adamantinoma metastases of 188 315
 - of jaws 311-315 (see also under *Dental tissues*)
 - of nasal cavity and sinuses 353-357
 - of pituitary region 315 628 629
 - of tibia 280-281 315
 - structure imitated 261 262 315 329 331
- Adenoacanthoma 537
- Adenocarcinoid 537
- Adenofibroma 99
- Adenoma (see under particular organs)
- Adenomyoma 542-544
- Adenosarcoma 220 925
- Adipose tissue tumours of (see *Lipoma and liposarcoma*)
- Adrenal cortex adenoma of 631 632 638
 - carcinoma of 631-634
 - heterotopic 453 503 507 710
 - hypernephroma of 631
 - hyperplasia of 634
 - secondary tumours of 631
 - tumours of 631-634
 - in animals 94-97 634
- Adrenal gland (see also *Adrenal cortex* and *Adrenal medulla*)
 - angioma of 708 709
 - melanoma of 915
 - secondary tumours of 178 242 297 303 342 368 374 410 426 430 431 449 463 477, 677 991
- Adrenal medulla chromaffin tumours of 47 710 837, 872-873
 - ganglioneuroma of (see *Neuroblastoma* and *Ganglioneuroma*)
 - neurominoma of 830-831
 - neuroblastoma of (see *Neuroblastoma*)
 - secondary tumours of 374 839
- Aerial metastasis 187-188 315
- Aetiological classification of tumours 15-16
- Age incidence of tumours 79-83 85 93 (and see under particular tumours)
- Albinism and tumours 55
- Albright's disease 678
- Alcohol as a cause of cancer 293 296 300 302 388 399
- Alimentary canal (and see under particular organs)
 - experimental tumours of 38 47
 - implantation metastases in 187
 - ingested carcinogens in 398-400 424
 - squamous metaplasia in 126
- Alveolar sarcoma 645
- Ameloblastoma (see *Adamantinoma* and *Dental tissues*)
- Ameloblasts 308-309
- Amines carcinogenic 46-47
- Aminoanthracene 47
- Aminoazotoluene 44-45 124
- Aminostilbene 47

INDEX

Carcinogenic hydrocarbons (*cont.*)

- applied simultaneously with Shope virus 60
- constitutional susceptibility to 40
- cumulative effect of 42
- discovery of 32-34
- effective amounts of 36
- effects of on lower animals plants 43
- formulae of principal 32
- ingestion of 37 38 399
- intravenous administration of 37-38
- lung tumours caused by 37-38 53-54 363-364
- metabolism of 40 43-44
- mode of action of 40-44
- neural tumours produced by 39
- occupational tumours due to 29 259 598-599
- pre neoplastic changes from 40-42
- relative potencies of 34-35
- remote action of 37-38 39-40
- sarcoma produced by 30-31 35-37 42
- search for 31-33
- single application effective 41
- solvents of 35
- tissue cultures affected by 43
- visceral tumours produced by 37-39

Carcinogenic parasites 57-60

Carcinoid tumour (see *Argentaffin carcinoma*)

Carcinoma (see also *Tumours* and under particular regions)

- age incidence of 79-83
- metastasis of by blood stream 172-178
 - by lymph stream 166-172
- mode of origin of 40-42 106-119
- sarcomatous change in stroma of 102 139 140-141
- sex incidence of 81 89
- simplex 238-239
- simulating other tumours 129-130 205 344-345 461-462 538 587 606 645
- spindle celled 270 296 343 367 369 529-530

Carcino-sarcoma 36 95 140-141 205 218 461 538 587 606 645 690

Carotid body tumours of 873-875

Cartilage tumours of (see *Chondroma* and *chondrosarcoma*)

Cartilaginous metaplasia (see *Metaplasia*)

Cat tumours in 96 226 266-267 306 318 361 387 420 433 445 510 597 654 655 690 713
780 796 820 915

Cattle (see *Bovines*)

Cauda equina tumours of 186 818

Causation of tumours 29-65

Cell inclusions in tumours 150 195 819

Cell rests 106 121 193-194 321-322 482 497 601 743 754 889

Cells (see *Tumours cells of Mitosis* etc.)

Cerebello pontine angle tumours of 638 824 828-829 832 838

Cerebrospinal fluid metastasis by 185-186 375 410 627 820 824-826
tumour cells in 186 627

Cerebrospinal spaces extension of tumours in 161-163 185-186 375 410 449-450 815-816
824-826 883-884 892 909 914

Ceruminous glands tumours of 95 286

Cervix uteri (see *Uterus*)

Cheek carcinoma of 298-299

salivary tumours of 323

Chemical carcinogens (see *Carcinogenic agents* and particular substances)

INDEX

Breast (*cont*)

fibro adenoma of (*cont*)

structure of 214-220 221

transplantable in rats 97 101 213

fibroma of 213 215

gynaecomastia of 246 581

mazoplasia of 214 230

mixed tumours of 218-220 755

myoblastoma of 743

Paget's disease of nipple dermal changes with 136

histogenesis of 248-252

Paget cells in 249-253

Paget's description of 247-248

structure of 249-253

papilloma of ducts 118 210 220-223 234

rhabdomyosarcoma of 755

sarcoma of 101 102 140 213 218-220 755

secondary tumours of 343 410

squamous metaplasia in 45 126 239

Brenner tumour 489-491

Broad ligament tumours of 492-493 698

Bromobenzene 43 44

Bronchus (*see Lung*)

Brooke's tumour 262 272 277

Brown Pearce rabbit tumour 99 101

Brunn's nests 471-472

Burns preceding cancer 123 260 263

Bursae tumours of 693-699

Butter yellow 44-45

Cachexia 25-27 144-145 203 210

Calcaneus myeloma of 786

Calcification in tumours 166 216 239 244 426 454 484 487 569 610 651-652 655 669

708 724-725 814 819 824 826 856

metastatic 640

Calcified epithelioma 271-272

Call Exner bodies 494-495

Cancer (*see Carcinoma etc*)

age 83

cures 103

definition of 66 67

en cuirasse 240 241

families 89-90 229 401 421-422 534 882-884

statistics 66-91

tests 145

Capillaries traversed by tumour cells 177

Carbohydrate metabolism of tumours 144

Carbon tetrachloride 46 124

Carcinogenesis experimental 29 65

Carcinogenic agents 29 65

endogenous formation of 51 55 61 232 435 439-440 597 937 970

excreted by skin 261-262

growth inhibited by 103 142 198

ingested 37 38 399 424

Carcinogenic amines 46-47

Carcinogenic azo-dyes 44-46

Carcinogenic hydrocarbons 29-44

applied simultaneously with actinic rays 55

INDEX

- Civet tumours in 445
- Civilization and cancer, 195-196
- Classification of tumours 9-18 202
- Clonorchis 434
- Co-carcinogenesis 35 42-44 194
- Coccygeal region chordoma of 910-923
teratoma of 943 952
- Coelenterates affected by carcinogens 43
- Coelomic cavities extension of tumours in 161 180-185 (see also *Peritonium* etc.)
- Cohnheim's cell rest hypothesis 106 123 193-194, 321-322, 482, 497, 601, 743 754 889
- Colchicine 23 103
- Collision tumour 140
- Colloid Cancer 130 239 (see also *Mucoid carcinoma*)
- Comedo cancer 237
- Composite tumours (see *Mixed tumours*)
- Compound names 16 321 643
- Condyloma 268
- Conjunctiva* carcinoma of 96, 262 265 266
melanoma of 910
naevus of 910
plasmocytoma of 790
- Contact cancers 187
- Cotton spinner's cancer 29 258 259 598-599
- Cranio-pharyngioma 628
- Creosote cancer 29 259 598
- Crocker tumour No. 10 140
- Crocodile tumours of 99
- Croton oil 43
- Cushing's syndrome 626 633-634
- Cylindroma, 321 336
- Cystadenocarcinoma 447 487
- Cystadenoma of breast 220-222
of ovary 483-487
of pancreas 443-444
- Cysticercus fasciolaris* 58
- Cystosarcoma phylloides 216
- Cysts (see under particular organs)
- Cytology of tumours 131-135
- Cytoma, 12
- Cytoplasm of tumour cells 41 43 133 197-200

- Dasyure tumours in 420
- Decidual reaction with chorionic tumours 131 991
- Deciduoma malignum 985
- Deelman phenomenon 30 42 395
- Deer tumours in* 524 841
- Definition of tumour 1-8 202
- Demodex folliculorum in skin tumours 262
- Dental defects in tumour causation 293 296 299 388 400
- Dental lamina 308-310
- Dental tissues adamantinoma of 310-315 318
ameloblastoma of (see *Adamantinoma* above)
classification of tumours of, 310-311
cysts of 311
development of 308-310
intra alveolar epidermoid carcinoma, 315-317
odontomes 310 317-318
- Dercum's disease 657

INDEX

- Chemistry of tumours 143-145 150
- Chemo-diagnosis of tumours 145
- Chemotherapy of tumours 102-103 143 206
- Chimney sweep's cancer 29 90 258 259 598-599
- Chloroma (Chloroleukaemia) 796-797
- Cholangioma 436
- Cholanthrene 32 33 36
- Cholesteatoma 826
- Cholesterol possible carcinogenic conversion of 55
- Cholic acid 33
- Chondrodysplasia 671
- Chondroma and chondrosarcoma 670-677
 - age incidence of 676
 - associated with angiomas 710
 - benign chondroblastoma 684
 - benign solitary chondroma 674-675
 - enchondrosis preceding 671 676
 - exostosis preceding 672 676
 - experimental 58
 - in animals 95 96 98 689-690
 - metastasis of 677
 - multiple 120 670-671
 - of lung 382-384
 - of soft tissues 648 688 689
 - osteoclastomatous 683-684
 - sex incidence of 674 676
 - sites of 676
 - structure of 676-677
 - veins invaded by 158 672
- Chordoma 918-923
- Chorio-adenoma 989
- Chorion-epithelioma 985 991
 - extra genital 985 986
 - hormonal results of 131 991
 - hydatidiform mole and 986-989
 - in animals 989
 - metastases of 176 990-991
 - stimulated by other tumours 129-130 404 436 474 559 575-577, 581 582 950 960 970 972 990
 - structure of 989-990
 - veins invaded by 989-990
- Choroid melanoma of 911-913
 - secondary tumours of 464
- Choroid plexus cysts of 824
 - lipoma of 658
 - papillary tumours of 185-186 818 824-826
 - psammoma of 824
 - secondary tumours of 185 622
- Chromaffin tumours 710 837 846 872-873
- Chromates as carcinogens 357-358 365
- Chromatophores 899
- Chromosomes of tumours 132-135
- Chronic irritation as a cause of tumours 47-48 56 194-195
- Chylous effusions 157 183
- Ciliary body tumours of 895-897
- Ciliated epithelium 628 956
- Circumcision 596-597
- Cisterna chyli invaded by tumours 156-157 170 171 407 447, 578